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(54) Title: 4-(PIPERIDYL- AND PYRROLIDYL-ALKYL-UREIDO)-QUINOLINES AS UROTENSIN II RECEPTOR ANTAGONISTS

(57) Abstract: The invention relates to novel 1-pyridin-4-yl urea derivatives and related compounds and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as neurohormonal antagonists.

NOVEL QUINOLINE DERIVATIVES

FIELD OF THE INVENTION

- 5 The present invention relates to novel 4-(piperidinyl- and pyrrolidinyl-alkyl-ureido)-quinoline derivatives of the general formula 1 and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of the general
10 formula 1 and especially their use as neurohormonal antagonists.

BACKGROUND OF THE INVENTION

Urotensin II is a cyclic 11-amino acid peptide neurohormone considered to be the most potent vasoconstrictor known, up to 28-fold more potent than endothelin-1. The effects of urotensin II are mediated through activation of a G-protein coupled
15 receptor, the UT receptor, also known as GPR14 or SENR (Ames RS, et al, "Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14" Nature (1999) 401, 282-6. Mori M, Sugo T, Abe M, Shimomura Y, Kurihara M, Kitada C, Kikuchi K, Shintani Y, Kurokawa T, Onda H, Nishimura O, Fujino M. "Urotensin II is the endogenous ligand of a G-protein-coupled orphan
20 receptor, SENR (GPR14)" Biochem. Biophys. Res. Commun. (1999) 265,123-9. Liu Q, Pong SS, Zeng Z, et al, "Identification of urotensin II as the endogenous ligand for the orphan G-protein-coupled receptor GPR14" Biochem. Biophys. Res. Commun. (1999) 266, 174-178.) Urotensin II and its receptor are conserved across evolutionarily distant species, suggesting an important physiological role for
25 the system (Bern HA, Pearson D, Larson BA, Nishioka RS. "Neurohormones from fish tails: the caudal neurosecretory system. I. Urophysiology and the caudal neurosecretory system of fishes" Recent Prog. Horm. Res. (1985) 41, 533-552). In euryhaline fish, urotensin II has an osmoregulatory role, and in mammals urotensin II exerts potent and complex hemodynamic actions. The response to

- urotensin II is dependent on the anatomical source and species of the tissue being studied. (Douglas SA, Sulpizio AC, Piercy V, Sarau HM, Ames RS, Aiyar NV, Ohlstein EH, Willette RN. "Differential vasoconstrictor activity of human urotensin-II in vascular tissue isolated from the rat, mouse, dog, pig, marmoset and cynomolgus monkey" Br. J. Pharmacol. (2000) 131, 1262-1274. Douglas, SA, Ashton DJ, Sauermelch CF, Coatney RW, Ohlstein DH, Ruffolo MR, Ohlstein EH, Aiyar NV, Willette R "Human urotensin-II is a potent vasoactive peptide: pharmacological characterization in the rat, mouse, dog and primate" J. Cardiovasc. Pharmacol. (2000) 36, Suppl 1:S163-6).
- 10 Like other neurohormones, urotensin II has growth stimulating and profibrotic actions in addition to its vasoactive properties. Urotensin II increases smooth muscle cell proliferation, and stimulates collagen synthesis (Tzandis A, et al, "Urotensin II stimulates collagen synthesis by cardiac fibroblasts and hypertrophic signaling in cardiomyocytes via G(alpha)q- and Ras-dependent pathways" J. Am. Coll. Cardiol. (2001) 37, 164A. Zou Y, Nagai R, and Yamazaki T, "Urotensin II induces hypertrophic responses in cultured cardiomyocytes from neonatal rats" FEBS Lett (2001) 508, 57-60). Urotensin II regulates hormone release (Silvestre RA, et al, "Inhibition of insulin release by urotensin II-a study on the perfused rat pancreas" Horm Metab Res (2001) 33, 379-81). Urotensin II has direct actions on atrial and ventricular myocytes (Russell FD, Molenaar P, and O'Brien DM "Cardiotonistulant effects of urotensin-II in human heart in vitro" Br. J. Pharmacol. (2001) 132, 5-9). Urotensin II is produced by cancer cell lines and its receptor is also expressed in these cells. (Takahashi K, et al, "Expression of urotensin II and urotensin II receptor mRNAs in various human tumor cell lines and secretion of urotensin II-like immunoreactivity by SW-13 adrenocortical carcinoma cells" Peptides (2001) 22, 1175-9). Urotensin II and its receptor are found in spinal cord and brain tissue, and intracerebroventricular infusion of urotensin II into mice induces behavioral changes (Gartlon J, et al, "Central effects of urotensin-II following ICV administration in rats" Psychopharmacology (Berlin) (2001) 155, 426-33).

Dysregulation of urotensin II is associated with human disease. Elevated circulating levels of urotensin II are detected in hypertensive patients, in heart

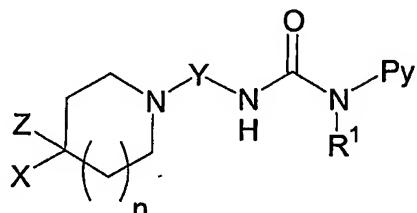
failure patients, and in patients awaiting kidney transplantation (Totsune K, et al, "Role of urotensin II in patients on dialysis" Lancet (2001) 358, 810-1).

Substances with the ability to block the actions of urotensin II are expected to prove useful in the treatment of various diseases. WO-2001/45694, WO-
5 2002/78641, WO-2002/78707, WO-2002/79155, and WO-2002/79188 disclose certain sulfonamides as urotensin II receptor antagonists, and their use to treat diseases associated with a urotensin II imbalance. WO-2001/45700 and WO-
10 2001/45711 disclose certain pyrrolidines or piperidines as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. These derivatives are different from the compounds of the present invention as they do not comprise urea derivatives bearing a 4-pyridinyl-like moiety. WO-2002/047687 discloses certain 2-amino-quinolones as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. WO-2002/058702 discloses certain 2-amino-quinolines as urotensin II
15 receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. These derivatives are different from the compounds of the present invention as they do not bear a substituted urea function in the 4-position of the quinoline ring. WO-2001/66143 discloses certain 2,3-dihydro-1H-pyrrolo[2,3-b]quinolin-4-ylamine derivatives useful as urotensin II receptor antagonists, WO-
20 2002/00606 discloses certain biphenyl compounds useful as urotensin II receptor antagonists, and WO-2002/02530 also discloses certain compounds useful as urotensin II receptor antagonists.

EP 428434 discloses certain alkylureidopyridines as neurokinin and substance P antagonists. WO-99/21835 discloses certain ureidoquinolines as H⁺-ATPase and
25 bone resorption inhibitors. WO-01/009088 discloses certain substituted heteroarylureas as inhibitors of the CCR-3 receptor. All of these ureidopyridine derivatives differ in their composition from compounds of the present invention. The present invention comprises N-(cyclic amino alkyl)-N'-pyridin-4-yl urea derivatives which are novel compositions of matter and which are useful as
30 urotensin II receptor antagonists.

DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the general formula 1.



General Formula 1

5 wherein:

Py represents pyridin-4-yl mono-substituted in position 2 with -NR²R³; pyridin-4-yl disubstituted in position 2 with -NR²R³ and in position 6 with lower alkyl or arylalkyl; unsubstituted quinolin-4-yl; quinolin-4-yl mono-substituted in position 2 with lower alkyl; quinolin-4-yl di-substituted in position 2 with lower alkyl and in 10 position 6, 7, or 8 with halogen, lower alkyl, or arylalkyl; 2-hydroxymethyl-quinolin-4-yl; 7-methyl-[1,8]naphthyridin-4-yl; 5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl; 8-benzyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl; 8-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl; 2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl; 1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl; 15 1-benzyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl;

15 b]pyridin-4-yl;

X represents aryl; aryl-O-; arylalkyl-; lower alkyl-SO₂NR²-; aryl-SO₂NR²-; arylalkyl-SO₂NR²-; lower alkyl-CONR²-; aryl-CONR²-; arylalkyl-CONR²-; lower alkyl-NR³CONR²-; aryl-NR³CONR²-; arylalkyl-NR³CONR²-; aryl-CO-; arylalkyl-CO-; lower alkyl-NR²CO-; aryl-NR²CO-; arylalkyl-NR²CO-; or X and Z represent together 20 with the carbon atom to which they are attached an exocyclic double bond which bears an aryl substituent.

Y represents -C(R⁴)(R⁵)(CH₂)_m- or -(CH₂)_mC(R⁴)(R⁵)-

Z represents hydrogen; in case X represents aryl or arylalkyl, Z represents hydrogen, hydroxyl, carboxyl, aryl-CONR²-; lower alkyl-NR²CO-, aryl-NR²CO- or 25 arylalkyl-NR²CO-;

n represents the numbers 0 or 1;

m represents the numbers 1 or 2;

R¹ represents hydrogen or lower alkyl;

R² and R³ represent independently hydrogen, lower alkyl, or arylalkyl; in case R²

and R³ are attached to the same nitrogen atom, R² and R³ together form with the

5 nitrogen to which they are attached, a piperidine, pyrrolidine or morpholine ring;

R⁴ represents hydrogen, lower alkyl, aryl, arylalkyl, or forms together with R⁵ a 3-,

4-, 5-, or 6-membered saturated carbocyclic ring including the carbon atom to

which R⁴ and R⁵ are attached as ring atoms;

R⁵ represents hydrogen, methyl, or forms together with R⁴ a 3-, 4-, 5-, or 6-

10 membered saturated carbocyclic ring including the carbon atom to which R⁴ and

R⁵ are attached as ring atoms;

and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates; as well as their pharmaceutically acceptable salts, solvent complexes,

15 and morphological forms.

In the definitions of the general formula 1 the expression 'aryl' means a substituted or unsubstituted aromatic carbocyclic or heterocyclic ring system, consisting of a five- or six- membered aromatic ring, or of a fused five-six or six-six aromatic ring system. Preferred aryl groups are for example 2-furyl; 2-thienyl; phenyl; 2-

20 methylphenyl; 2-biphenyl; 2-methoxyphenyl; 2-phenoxyphenyl; 2-chlorophenyl; 2-

bromophenyl; 2-*i*-propylphenyl; 2-fluorophenyl; 2-methylsulfonylphenyl; 2-

cyanophenyl; 2-trifluoromethylphenyl; 3-methylphenyl; 3-biphenyl; 3-

phenoxyphenyl; 3-methoxyphenyl; 3-chlorophenyl; 3-bromophenyl; 3-fluorophenyl;

3-cyanophenyl; 3-trifluoromethylphenyl; 3-carboxyphenyl; 4-methylphenyl; 4-

25 ethylphenyl; 4-*i*-propylphenyl; 4-phenyloxyphenyl; 4-trifluoromethylphenyl; 4-

trifluoromethoxyphenyl; 4-phenoxyphenyl; 4-cyanophenyl; 4-hydroxyphenyl; 4-

acetylaminophenyl; 4-methanesulfonylphenyl; 4-*n*-propylphenyl; 4-*iso*-

propylphenyl; 4-*tert*-butylphenyl; 4-*n*-pentylphenyl; 4-biphenyl; 4-chlorophenyl; 4-

bromophenyl; 4-bromo-2-ethylphenyl; 4-fluorophenyl; 2,4-difluorophenyl; 4-*n*-

butoxyphenyl; 2,6-dimethoxyphenyl; 3,5-bis-trifluoromethylphenyl; 2-pyridyl; 3-pyridyl; 4-pyridyl; 1-naphthyl; 2-naphthyl; 4-(pyrrol-1-yl)phenyl; 4-benzoylphenyl; 5-dimethylaminonaphth-1-yl; 5-chloro-3-methylthiophen-2-yl; 5-chloro-3-methylbenzo[b]thiophen-2-yl; 3-(phenylsulfonyl)-thiophen-2-yl; 2-(2,2,2-trifluoroacetyl)-1-
5 2,3,4-tetrahydroisoquinolin-7-yl; 4-(3-chloro-2-cyanophenoxy)phenyl; 2-(5-benzamidomethyl)thiophenyl; 4,5-dichlorothien-2-yl; 5-quinolyl; 6-quinolyl; 7-quinolyl; 8-quinolyl; (2-acetylamino-4-methyl)thiazol-5-yl; or 1-methylimidazol-4-yl.

In the definitions of the general formula 1 the expression 'lower alkyl' means a saturated straight chain, branched chain or cyclic substituent consisting of from
10 one to eight carbons, comprising methyl, ethyl, n-propyl, 3-allyl, iso-propyl, n-butyl, iso-butyl, n-pentyl, n-hexyl, n-octyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl and the like. Preferred lower alkyl groups are methyl, ethyl, and n-propyl.

In the definitions of the general formula 1 the expression 'arylalkyl' means a C1 to
15 C3 group bearing an aryl group, where 'aryl' has the meaning given above.

The present invention encompasses pharmaceutically acceptable salts of compounds of the general formula 1. This encompasses either salts with inorganic acids or organic acids like hydrohalogenic acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid,
20 maleic acid, tartaric acid, methylsulfonic acid, p-tolylsulfonic acid and the like or in case the compound of formula 1 is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium, potassium, or calcium salts, etc. The compounds of general formula 1 can also be present in form of zwitterions.

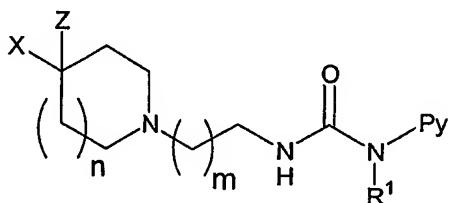
The present invention encompasses different solvation complexes of compounds of general formula 1. The solvation can be effected in the course of the manufacturing process or can take place separately, e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of general formula 1.

The present invention further encompasses different morphological forms, e.g. crystalline forms, of compounds of general formula 1 and their salts and solvation complexes. Particular heteromorphs may exhibit different dissolution properties,

stability profiles, and the like, and are all included in the scope of the present invention.

The compounds of the general formula 1 might have one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates. The present invention encompasses all these forms. They are prepared by stereoselective synthesis, or by separation of mixtures in a manner known per se, i.e. by column chromatography, thin layer chromatography, HPLC, crystallization, etc.

10 Preferred compounds of the invention are compounds of the general formula 2.



General Formula 2

wherein:

- Py represents 2-(benzyl-methyl-amino)-pyridin-4-yl; 2-(benzyl-methyl-amino)-6-
15 methyl-pyridin-4-yl; 2-(benzylamino)-pyridin-4-yl; 2-benzylamino-6-methyl-pyridin-
4-yl; 2-(dimethylamino)-pyridin-4-yl; 2-(dimethylamino)-6-methyl-pyridin-4-yl; 2-
(methylamino)-pyridin-4-yl; 2-(methylamino)-6-methyl-pyridin-4-yl; 2-aminopyridin-
4-yl; 2-amino-6-methyl-pyridin-4-yl; 2-(pyrrolidin-1-yl)-pyridin-4-yl; quinol-4-yl; 2-
methylquinol-4-yl; 2-cyclopropylquinol-4-yl; 8-benzyl-2-methyl-quinol-4-yl;
20 [1,8]naphthyridin-4-yl; 7-methyl-[1,8]naphthyridin-4-yl; 5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl; 8-benzyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl; 8-methyl-
5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl; 2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl;
1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl; 1-benzyl-2,3-dihydro-1H-
pyrrolo[2,3-b]pyridin-4-yl;
- 25 X represents aryl; aryl-O-; arylalkyl-; lower alkyl-SO₂NR²-; aryl-SO₂NR²-; arylalkyl-
SO₂NR²-; lower alkyl-CONR²-; aryl-CONR²-; arylalkyl-CONR²-; lower alkyl-

$\text{NR}^3\text{CONR}^2-$; aryl-NR $^3\text{CONR}^2-$; arylalkyl-NR $^3\text{CONR}^2-$; aryl-CO-; arylalkyl-CO-; lower alkyl-NR $^2\text{CO}-$; aryl-NR $^2\text{CO}-$; arylalkyl-NR $^2\text{CO}-$;

Z represents hydrogen; in case X represents aryl or arylalkyl, Z represents hydrogen or hydroxyl;

5 n represents the numbers 0 or 1;

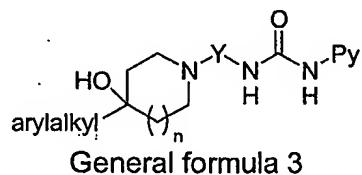
m represents the numbers 1 or 2;

R 1 represents hydrogen or lower alkyl;

R 2 and R 3 represent independently hydrogen, lower alkyl, or arylalkyl;

Preferred compounds of general formula 1 are the compounds of general formula

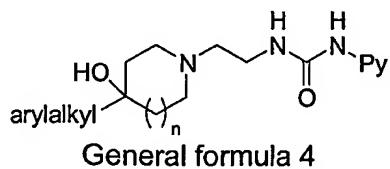
10 3:



wherein n, Y and Py have the meaning given in general formula 1.

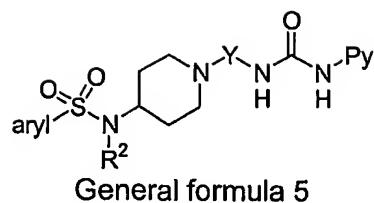
Preferred compounds of general formula 1 are the compounds of general formula

15 4:



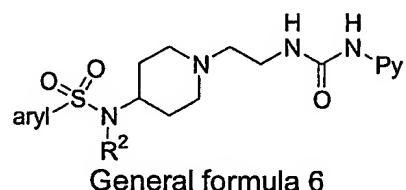
wherein n and Py has the meaning given in general formula 2.

20 Preferred compounds of general formula 1 are the compounds of general formula
5:



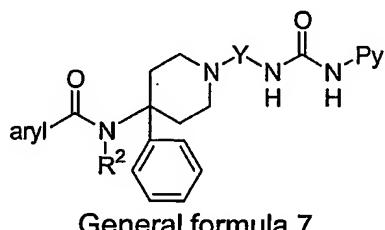
wherein R², Y and Py have the meaning given in general formula 1.

5 Preferred compounds of general formula 1 are the compounds of general formula
6:



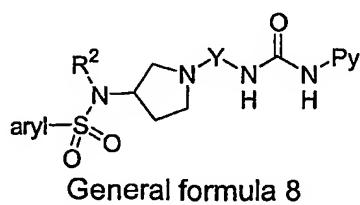
wherein R² and Py have the meaning given in general formula 2.

10 Preferred compounds of general formula 1 are the compounds of general formula
7:



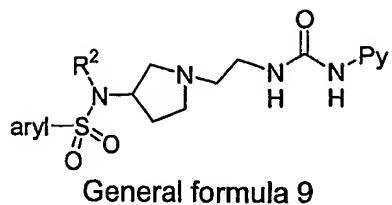
wherein R², Y and Py have the meaning given in general formula 1.

15 Preferred compounds of general formula 1 are the compounds of general formula
8:



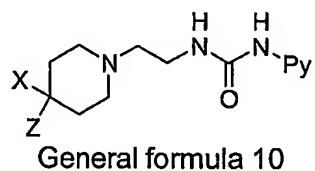
wherein R², Y and Py have the meaning given in general formula 1.

20 Preferred compounds of general formula 1 are the compounds of general formula
9:



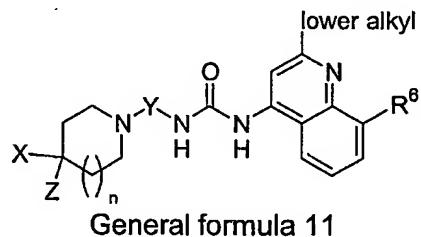
wherein R² and Py have the meaning given in general formula 2.

Preferred compounds of general formula 1 are the compounds of general formula 10:



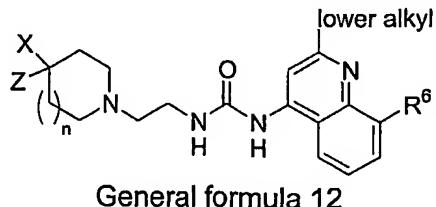
wherein X, Z and Py have the meaning given in general formula 1.

Preferred compounds of general formula 1 are the compounds of general formula 11:



wherein R⁶ is hydrogen, lower alkyl, or arylalkyl; and n, X, Y, and Z have the meaning given in general formula 1.

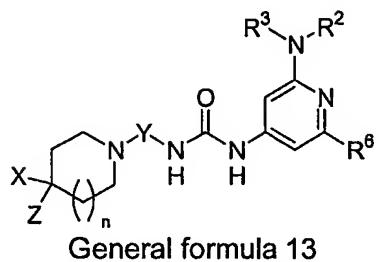
Preferred compounds of general formula 1 are the compounds of general formula 12:



wherein R⁶ has the meaning given in general formula 11; and n, X and Z have the meaning given in general formula 2.

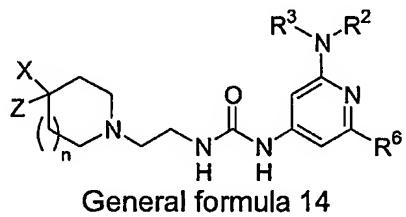
20 meaning given in general formula 2.

Preferred compounds of general formula 1 are the compounds of general formula 13:



- 5 wherein R⁶ has the meaning given in general formula 11; and n, R², R³, X, Y, and Z have the meaning given in general formula 1.

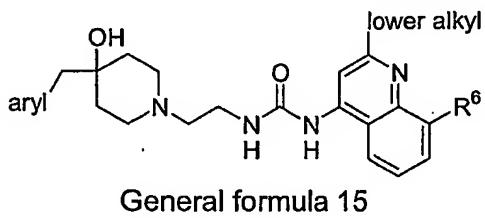
Preferred compounds of general formula 1 are the compounds of general formula 14:



10

- wherein R⁶ has the meaning given in general formula 11; and n, R², R³, X and Z have the meaning given in general formula 1.

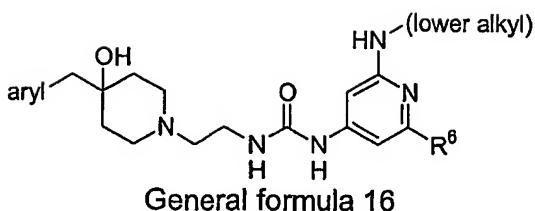
Preferred compounds of general formula 1 are the compounds of general formula 15:



15

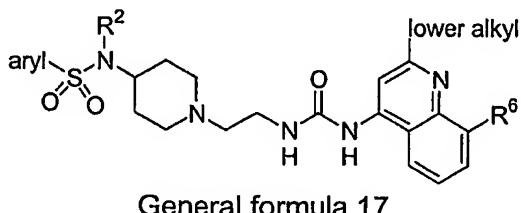
- wherein R⁶ has the meaning given in general formula 11.

Preferred compounds of general formula 1 are the compounds of general formula 16:



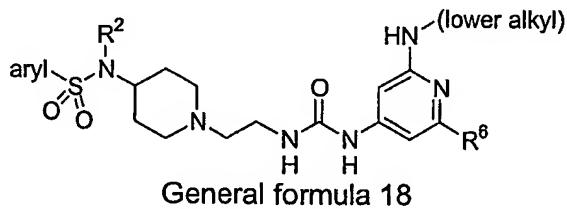
wherein R⁶ has the meaning given in general formula 11.

Preferred compounds of general formula 1 are the compounds of general formula 17:



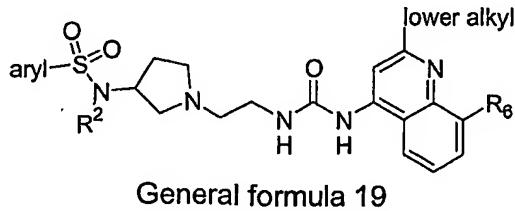
wherein R⁶ has the meaning given in general formula 11; and R² has the meaning given in general formula 1.

Preferred compounds of general formula 1 are the compounds of general formula 18:



wherein R⁶ has the meaning given in general formula 11; and R² has the meaning given in general formula 1.

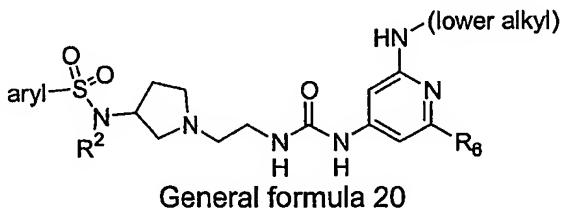
Preferred compounds of general formula 1 are the compounds of general formula 19:



wherein R⁶ has the meaning given in general formula 11; and R² has the meaning given in general formula 1.

Preferred compounds of general formula 1 are the compounds of general formula 20:

5



wherein R⁶ has the meaning given in general formula 11; and R² has the meaning given in general formula 1.

Examples of particularly preferred compounds of general formula 1 are selected
10 from the group consisting of:

| Example Number | |
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| 1. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethyl-benzenesulfonamide |
| 3. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 5. | Thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 8. | 3-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 9. | 3,N-Dimethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 11. | 2-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |

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| 12. | 2,N-Dimethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 13. | 4-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 14. | 4-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 15. | 4,N-Dimethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 17. | 2-Fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 18. | 2-Fluoro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 21. | 3-Fluoro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 24. | 4-Fluoro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 31. | 4-Cyano-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 35. | 3-Methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 36. | 3-Methoxy-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 37. | 4-Methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 38. | 4-Methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |

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| | pyrrolidin-3-yl)-benzenesulfonamide |
| 39. | 4-Methoxy-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 41. | 3-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 42. | 3-Chloro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 43. | 4-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 44. | 4-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 46. | 2-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 55. | Biphenyl-4-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 57. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-propyl-benzenesulfonamide |
| 58. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-propyl-benzenesulfonamide |
| 62. | Naphthalene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide |
| 63. | Naphthalene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 64. | Naphthalene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |

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| 65. | Naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide |
| 66. | Naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 67. | Naphthalene-1-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 69. | Quinoline-8-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 70. | Quinoline-8-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 72. | 4-tert-Butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 73. | 4-tert-Butyl-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 77. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethyl-benzenesulfonamide |
| 78. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethyl-benzenesulfonamide |
| 79. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-trifluoromethyl-benzenesulfonamide |
| 80. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-trifluoromethyl-benzenesulfonamide |
| 81. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-trifluoromethyl-benzenesulfonamide |
| 83. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-3-trifluoromethyl-benzenesulfonamide |

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| | trifluoromethyl-benzenesulfonamide |
| 85. | 3,4-Dichloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 87. | 3,4-Dichloro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 88. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-pentyl-benzenesulfonamide |
| 89. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-pentyl-benzenesulfonamide |
| 90. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-pentyl-benzenesulfonamide |
| 92. | 4-Butoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 93. | 4-Butoxy-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 94. | 4,5-Dichloro-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide |
| 95. | 4,5-Dichloro-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 96. | 4,5-Dichloro-thiophene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 97. | 4-(3-Chloro-2-cyano-phenoxy)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 98. | 4-(3-Chloro-2-cyano-phenoxy)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |

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| 99. | 4-(3-Chloro-2-cyano-phenoxy)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 103. | N-[4-Methyl-5-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)sulfamoyl]-thiazol-2-yl]-acetamide |
| 106. | 3-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 107. | 3-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 108. | 3-Bromo-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 109. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 110. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 111. | 4-Bromo-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 113. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-trifluoromethoxy-benzenesulfonamide |
| 115. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethoxy-benzenesulfonamide |
| 116. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethoxy-benzenesulfonamide |
| 117. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethoxy-benzenesulfonamide |
| 118. | 5-Dimethylamino-naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide |

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| | quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide |
| 119. | 5-Dimethylamino-naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 120. | 5-Dimethylamino-naphthalene-1-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 121. | 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide |
| 122. | 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 123. | 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 124. | 4-Bromo-2-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 125. | 4-Bromo-2-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 126. | 4-Bromo-2-ethyl-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 130. | N-[5-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)sulfamoyl]-thiophen-2-ylmethyl]-benzamide |
| 131. | N-[5-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)sulfamoyl]-thiophen-2-ylmethyl]-benzamide |
| 132. | N-[5-[Methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-sulfamoyl]-thiophen-2-ylmethyl]-benzamide |
| 133. | 4-Benzenesulfonyl-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide |

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| 134. | 4-Benzenesulfonyl-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 135. | 4-Benzenesulfonyl-thiophene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 136. | 2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide |
| 137. | 2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 138. | 2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide |
| 141. | 2-Phenyl-ethanesulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide |
| 142. | 4-Chloro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 144. | 4-Bromo-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 174. | 1-{2-[4-(3-Biphenyl-2-yl-ureido)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea |
| 175. | 1-{2-[3-(3-Biphenyl-2-yl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea |
| 239. | 1-(2-{4-[3-(2-Isopropyl-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea |

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| 240. | 1-(2-{3-[3-(2-Isopropyl-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea |
| 249. | 1-(2-Methyl-quinolin-4-yl)-3-(2-{3-[3-(2-phenoxy-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-urea |
| 275. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-naphthalen-1-yl-acetamide |
| 341. | 2-(4-Bromo-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide |
| 346. | 4-Benzoyl-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide |
| 365. | 1-(2-Methyl-quinolin-4-yl)-3-[2-(4-phenyl-piperidin-1-yl)-ethyl]-urea |
| 367. | 1-(2-Methyl-quinolin-4-yl)-3-[2-(4-o-tolyl-piperidin-1-yl)-ethyl]-urea |
| 369. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea |
| 370. | 1-[2-(4-Hydroxy-4-phenyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea |
| 376. | 1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea |
| 437. | 1-[2-(Benzyl-methyl-amino)-pyridin-4-yl]-3-[2-(4-benzyl-piperidin-1-yl)-ethyl]-urea |

Examples of preferred compounds of general formula 1 are selected from the list consisting of:

| Example Number | |
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| 143. | 4-Bromo-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 145. | 4-Bromo-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 146. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-N-propyl-benzenesulfonamide |
| 147. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-N-propyl-benzenesulfonamide |
| 148. | 4-Bromo-N-isobutyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 149. | 4-Bromo-N-isobutyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 150. | 4-Bromo-N-butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 151. | 4-Bromo-N-butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 152. | N-Benzyl-4-bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 153. | N-Benzyl-4-bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 154. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-N-phenethyl-benzenesulfonamide |
| 155. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-N-phenethyl-benzenesulfonamide |
| 156. | 4-Bromo-N-methyl-N-((R)-1-[2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |

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| | ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 157. | 4-Bromo-N-ethyl-N-((R)-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 158. | 4-Bromo-N-ethyl-N-((S)-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 159. | 4-Bromo-N-methyl-N-((S)-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide |
| 160. | N-Ethyl-3-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 161. | N-Ethyl-4-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 162. | N-Ethyl-2-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 163. | 3-Chloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 164. | 2-Chloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 165. | 4-Chloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 166. | N-Ethyl-4-fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 167. | N-Ethyl-4-methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |
| 168. | 3,4-Dichloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide |

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| 169. | N-Ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethyl-benzenesulfonamide |
| 230. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[4-(3-phenethyl-ureido)-piperidin-1-yl]-ethyl}-urea |
| 384. | 1-[(S)-1-(4-Benzyl-piperidin-1-ylmethyl)-2-methyl-propyl]-3-(2-methyl-quinolin-4-yl)-urea |
| 385. | 1-[(S)-1-Benzyl-2-(4-benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea |
| 386. | 1-[(S)-1-(4-Benzyl-piperidin-1-ylmethyl)-3-methyl-butyl]-3-(2-methyl-quinolin-4-yl)-urea |
| 389. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-cyclopropyl-quinolin-4-yl)-urea |
| 392. | 1-{2-[4-(3-Methyl-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea |
| 394. | 1-{2-[4-(2-Methyl-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea |
| 395. | 1-{2-[4-(4-Methoxy-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea |
| 396. | 1-{2-[4-(4-Fluoro-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea |
| 397. | 1-{2-[4-(4-Bromo-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea |
| 398. | 1-{2-[4-(3-Methyl-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea |
| 399. | 1-{2-[4-(2-Methyl-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea |

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| | quinolin-4-yl)-urea |
| 401. | 1-{2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea |
| 412. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-phenyl-amide |
| 416. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid (2-chloro-phenyl)-methyl-amide |
| 425. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide |
| 427. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid methyl-phenethyl-amide |
| 428. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-ethyl-amide |
| 429. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid dimethylamide |
| 432. | 4-Benzyl-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-ethyl-amide |
| 447. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methylamino-pyridin-4-yl)-urea |
| 448. | 1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methylamino-pyridin-4-yl)-urea |

Because of their ability to inhibit the actions of urotensin II, the described compounds can be used for treatment of diseases which are associated with an increase in vasoconstriction, proliferation or other disease states associated with the actions of urotensin II. Examples of such diseases are hypertension,

atherosclerosis, angina or myocardial ischemia, congestive heart failure, cardiac insufficiency, cardiac arrhythmias, renal ischemia, chronic kidney disease, renal failure, stroke, cerebral vasospasm, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, diabetes, diabetic arteriopathy, diabetic nephropathy,

5 connective tissue diseases, cirrhosis, asthma, chronic obstructive pulmonary disease, high-altitude pulmonary edema, Raynaud's syndrome, portal hypertension, thyroid dysfunction, pulmonary edema, pulmonary hypertension, or pulmonary fibrosis. They can also be used for prevention of restenosis after balloon or stent angioplasty, for the treatment of cancer, prostatic hypertrophy,

10 erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, sickle cell acute chest syndrome, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, addictions,

15 schizophrenia, Alzheimer's disease, anxiety, obsessive-compulsive behavior, epileptic seizures, stress, depression, dementias, neuromuscular disorders, neurodegenerative diseases, as well as other diseases related to a dysregulation of urotensin II or urotensin II receptors.

These compositions may be administered in enteral or oral form e.g. as tablets,

20 dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form like sprays and aerosols, or rectally in form of suppositories. These compounds may also be administered in intramuscular, parenteral or intravenous form, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of formula 1 as

25 well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients, which are usual in the pharmaceutical industry, like lactose, maize or derivatives thereof, talcum, stearic acid or salts of these materials.

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols etc.

30 may be used. For the preparation of solutions and sirups e.g. water, polyols, saccharose, glucose etc. are used. Injectables are prepared by using e.g. water,

polyols, alcohols, glycerin, vegetable oils, lecithin, liposomes etc. Suppositories are prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols etc.

The compositions may contain in addition preservatives, stabilisation improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, anti-oxidants etc.

The compounds of general formula 1 may also be used in combination with one or more other therapeutically useful substances e.g. α- and β-blockers like phenolamine, phenoxybenzamine, atenolol, propranolol, timolol, metoprolol, carteolol, carvedilol, etc.; with vasodilators like hydralazine, minoxidil, diazoxide, flosequinan, etc.; with calcium-antagonists like diltiazem, nicardipine, nimodipine, verapamil, nifedipine, etc.; with angiotensin converting enzyme-inhibitors like cilazapril, captopril, enalapril, lisinopril etc.; with potassium channel activators like pinacidil, chromakalim, etc.; with angiotensin receptor antagonists like losartan, valsartan, candesartan, irbesartan, eprosartan, telmisartan, and tasosartan, etc.; with diuretics like hydrochlorothiazide, chlorothiazide, acetolamide, bumetanide, furosemide, metolazone, chlortalidone, etc.; with sympatholytics like methyldopa, clonidine, guanabenz, reserpine, etc.; with endothelin receptor antagonists like bosentan, tezosentan, darusentan, atrasentan, enräsentan, or sitaxsentan, etc.; with anti-hyperlipidemic agents like lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, simvastatin, etc.; and other therapeutics which serve to treat high blood pressure, vascular disease or other disorders listed above.

The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given daily in oral form should be between about 25 3 mg and about 3 g, preferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses of equal weight per day. As usual children should receive lower doses which are adapted to body 30 weight and age.

GENERAL PREPARATION OF COMPOUNDS OF THE INVENTION

Compounds of the general formula 1 can be prepared using methods generally known in the art, according to the general sequence of reactions outlined below.

For simplicity and clarity reasons sometimes only a few of the possible synthetic

5 routes that lead to compounds of general formula 1 are described.

For the synthesis of compounds of general formula 1 general synthetic routes illustrated in Schemes A through E can be employed. The generic groups Py, R¹, R², R³, X, Z, Y, n, and m employed in Schemes A through E have the definitions given in general formula 1 above. Other abbreviations used are defined in the

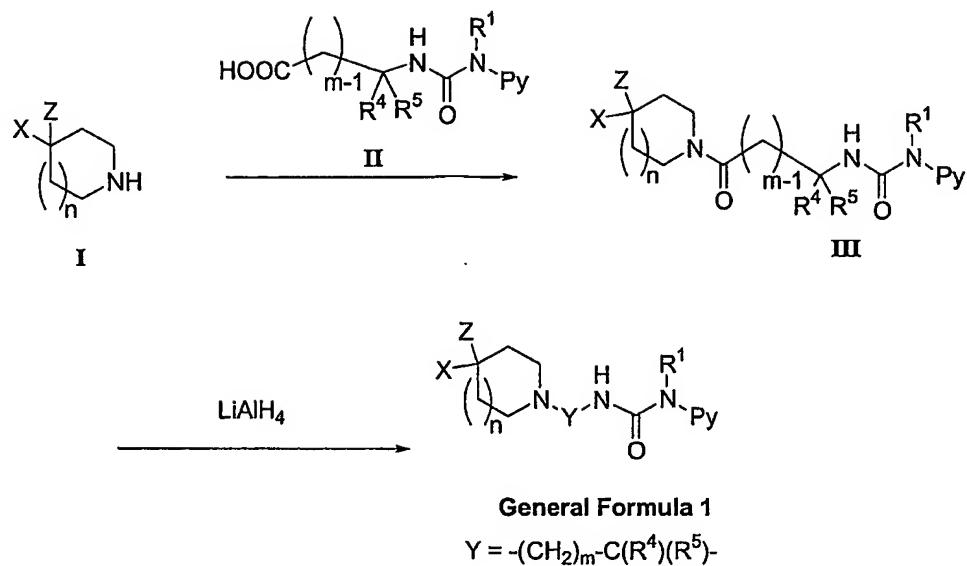
10 Experimental Section. Some instances of the generic groups X and Z might be incompatible with the assembly illustrated in Schemes A through E and so will require the use of protecting groups. The use of protecting groups is well known in the art (see for example "Protective Groups in Organic Synthesis", T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999). For the purposes of this discussion, it will

15 be assumed that such protecting groups as are necessary are in place.

Preparation of compounds of general formula 1 wherein Y is -(CH₂)_mC(R⁴)(R⁵)-

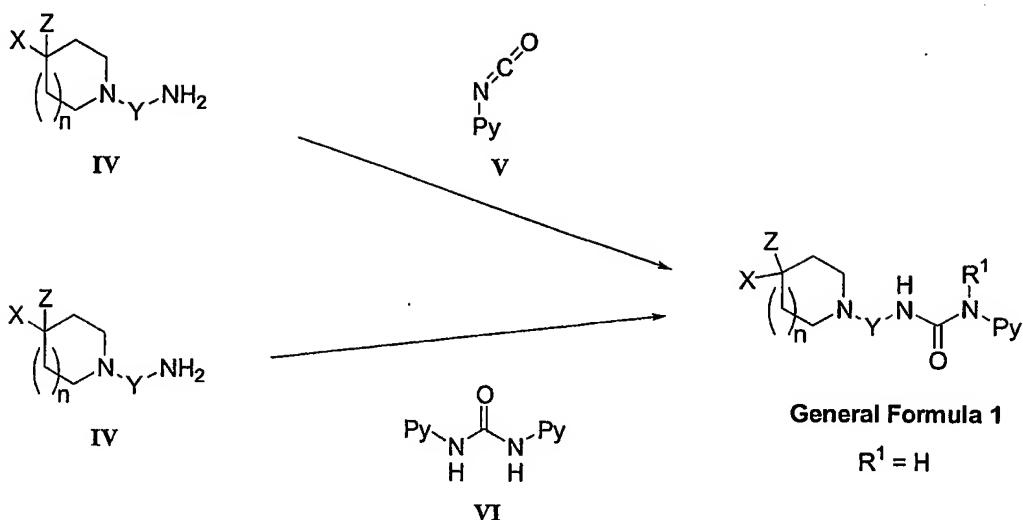
Compounds of general formula 1 wherein Y is -(CH₂)_mC(R⁴)(R⁵)- are prepared according to Scheme A. Compounds of general formula 1 wherein Y is -C(R⁴)(R⁵)-(CH₂)_m- are prepared according to Scheme B.

Scheme A



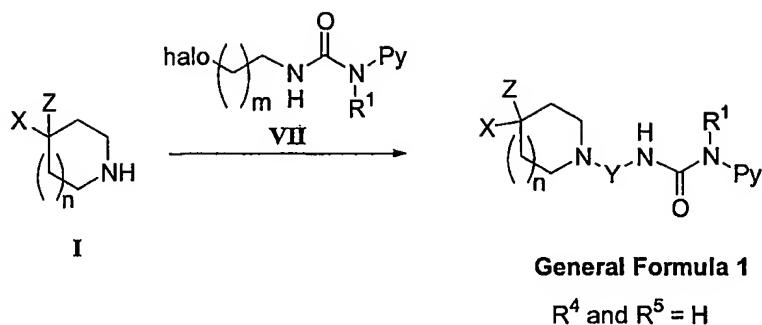
- 4-Substituted-piperidines and 3-substituted-pyrrolidines of general structure I in Scheme A are either commercially available in racemic or optically active form or
 5 are prepared in racemic or optically active form by methods well known in the art.
 Ureido acetic- and propionic acid derivatives of general structure II in Scheme A are prepared according to Scheme F below. N-Acylation of piperidines and pyrrolidines of general structure I with ureido acetic- and propionic acid derivatives of general structure II is accomplished in a polar solvent such as DMF in the
 10 presence of a small stoichiometric excess of a coupling reagent such as a carbodiimide to provide amides of general structure III. Selective reduction of the amide carbonyl group with a reagent such as LiAlH₄ in a polar solvent such as THF provides the target compounds of general formula 1 wherein Y is -
 (CH₂)_mC(R⁴)(R⁵).
 15 Preparation of compounds of general formula 1 wherein R¹ is H. These compounds are alternatively prepared according to Scheme B.

Scheme B



- Amines of general structure **IV** are reacted with isocyanates of general structure **V** or ureas of general structure **VI** to provide the final compounds of general formula 1 wherein R^1 is H. Alternatively, amines of general structure **IV** are reacted with ureas of general structure **VI** to provide the final compounds of general formula 1 wherein R^1 is H. The preparation of isocyanates of general structure **V** and of ureas of general structure **VI** is described in Scheme E below. The preparation of amines of general structure **IV** is described in Scheme G below.
- 10 Compounds of general formula 1 wherein R^4 and R^5 are H. These compounds are prepared according to the method illustrated in Scheme C.

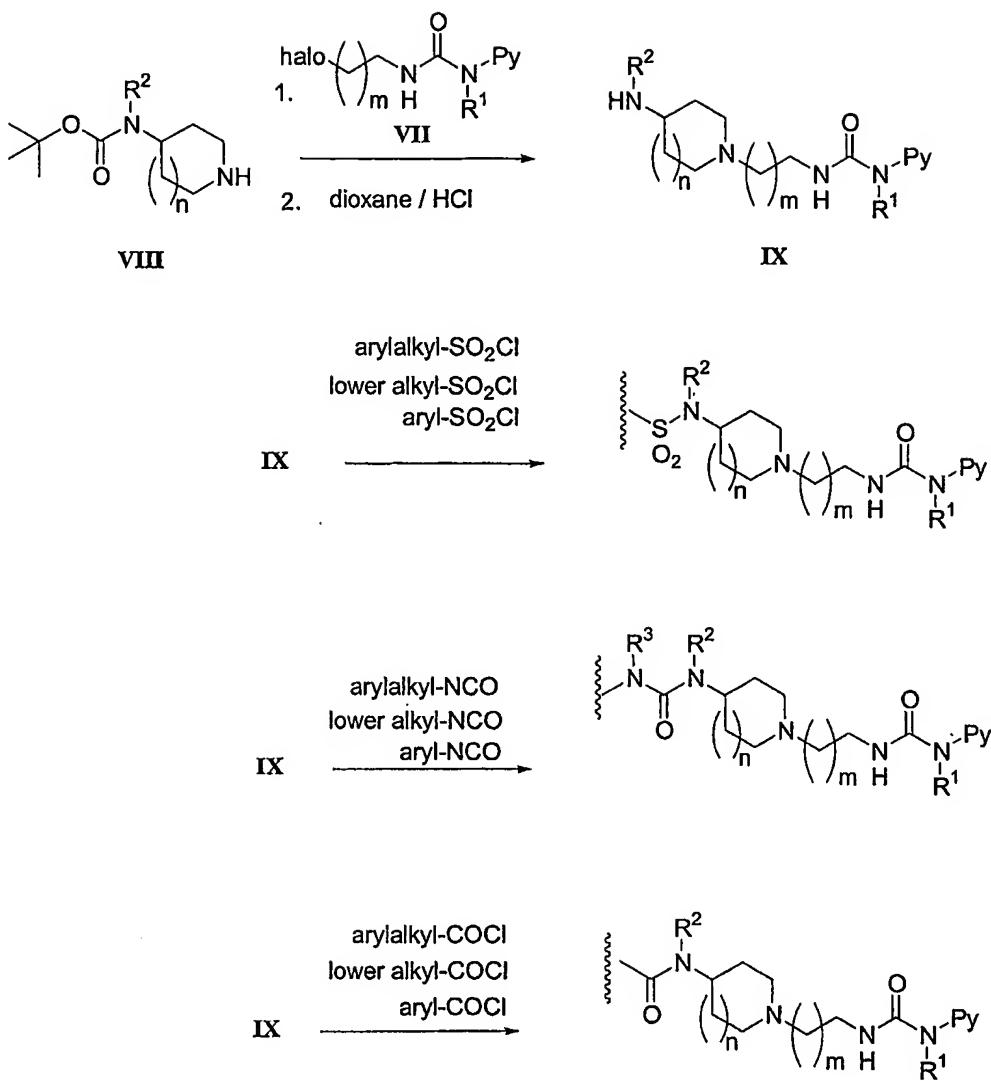
Scheme C



4-Substituted-piperidines and 3-substituted-pyrrolidines of general structure I in Scheme C are either commercially available in racemic or optically active form or
 5 are prepared in racemic or optically active form by methods well known in the art.
 Haloalkyl ureas of general structure VII in Scheme C are prepared according to Scheme E below. N-Alkylation of piperidines and pyrrolidines of general structure I with haloalkyl ureas of general structure VII is accomplished in a polar solvent such as tetrahydrofuran in the presence of a sub-stoichiometric amount of an
 10 iodide salt such as NaI and a small stoichiometric excess of acid scavenger such as Na_2CO_3 , to provide the target compounds of general formula 1.

Compounds of general formula 1 wherein X represents lower alkyl- SO_2NR^2 -; aryl- SO_2NR^2 -; arylalkyl- SO_2NR^2 -; lower alkyl- CONR^2 -; aryl- CONR^2 -; arylalkyl- CONR^2 -; lower alkyl- NR^3CONR^2 -; aryl- NR^3CONR^2 -; arylalkyl- NR^3CONR^2 -; and Z, R^4 and R^5 represent H. These compounds are alternatively prepared according to the method illustrated in Scheme D.

Scheme D

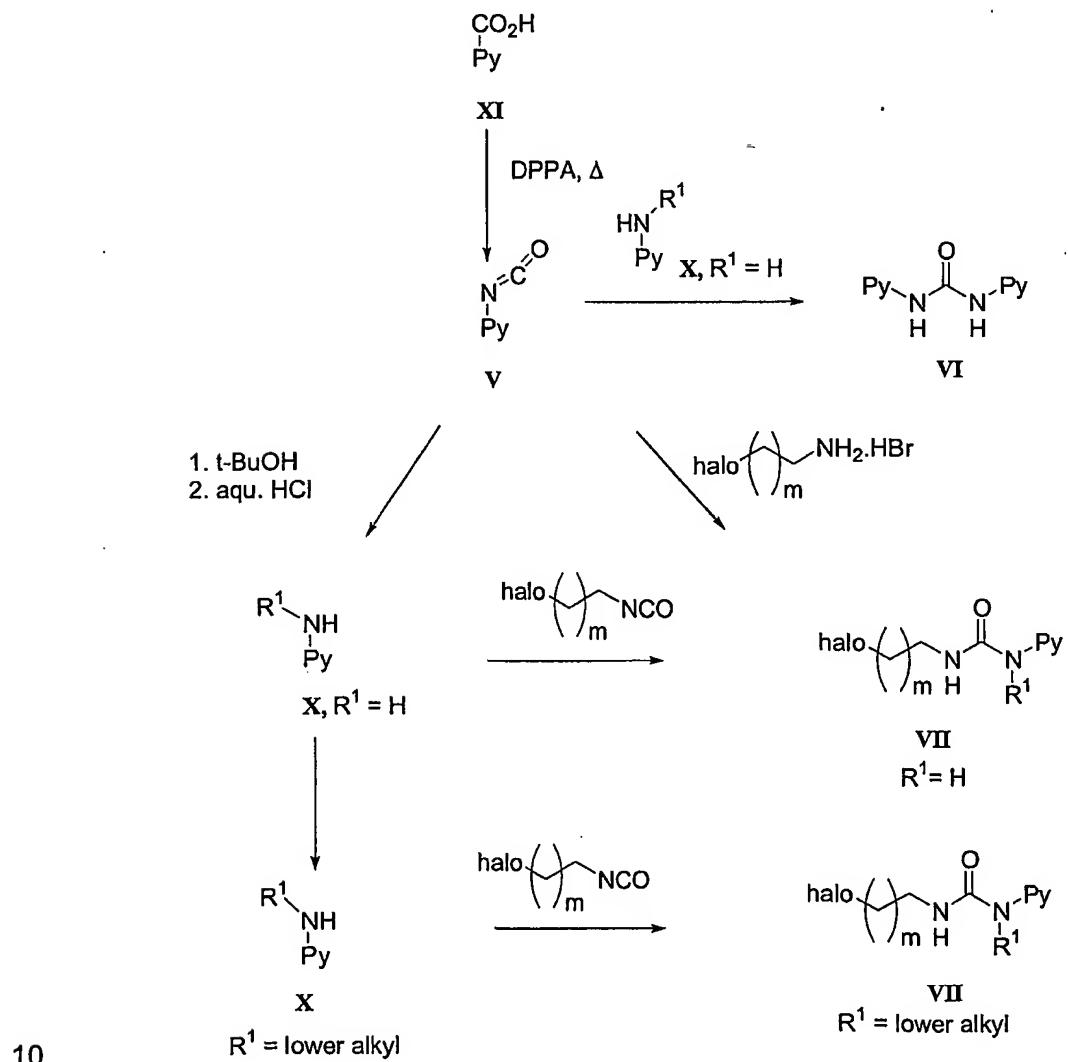


Racemic or chiral carbamates of general structure **VIII** are either commercially available or readily prepared by methods well known in the art. Haloalkyl ureas of general structure **VII** are prepared according to Scheme E below. Carbamates of general structure **VIII** are reacted with haloalkyl ureas of general structure **VII** in a polar solvent such as tetrahydrofuran in the presence of a substoichiometric amount of an iodide salt such as NaI and a small stoichiometric excess of an acid scavenger such as Na_2CO_3 , followed by removal of the carbamate group under acidic conditions, such as reaction with TFA in CH_2Cl_2 . The resulting compounds of general structure **IX** are converted to final compounds of general formula 1

wherein lower alkyl-SO₂NR²-; aryl-SO₂NR²-; arylalkyl-SO₂NR²-; lower alkyl-CONR²-; aryl-CONR²-; arylalkyl-CONR²-; lower alkyl-NR³CONR²-; aryl-NR³CONR²-; arylalkyl-NR³CONR²-; and Z, R⁴ and R⁵ represent H, by reaction with commercially available or well known sulfonylchlorides, isocyanates, or acid chlorides.

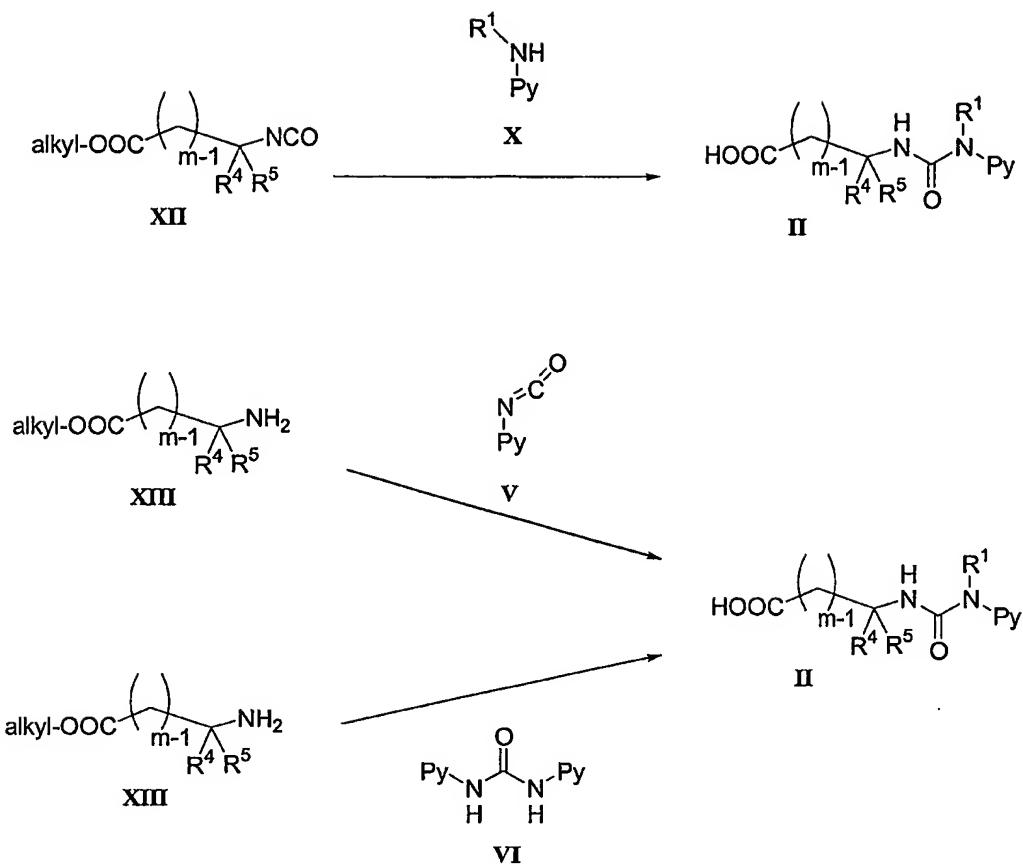
Synthetic intermediates used in Schemes A, B, C, and D. Synthetic intermediates containing the group Py, as defined in the general formula 1 above, are obtained by the methods illustrated in Scheme E and F.

Scheme E



Carboxylic acids of general structure XI are commercially available or are prepared by well known methods. Reaction with diphenylphosphorylazide provides the acyl azide, which undergoes Curtius rearrangement to provide the isocyanates of general structure V, which are used in situ. Isocyanates of general structure V, 5 reacted with halopropylamine hydrochloride or haloethylamine hydrochloride in the presence of an acid scavenger such as DIPEA, provide ureas of general structure VII wherein R¹ is H. Isocyanates of general structure V are reacted with tert-butanol to provide the corresponding carbamoyl ester, which is hydrolyzed with aqueous acid such as HCl, to provide amines of general structure X where R¹ is H. 10 Alkylation by one of several methods well known in the art, such as reductive amination with a suitable lower aldehyde provides secondary amines of general structure X. Reaction of amines of general structure X with commercially available chloroethylisocyanate or chloropropylisocyanate in a polar aprotic solvent such as tetrahydrofuran provides the ureas of general structure VII.

Scheme F

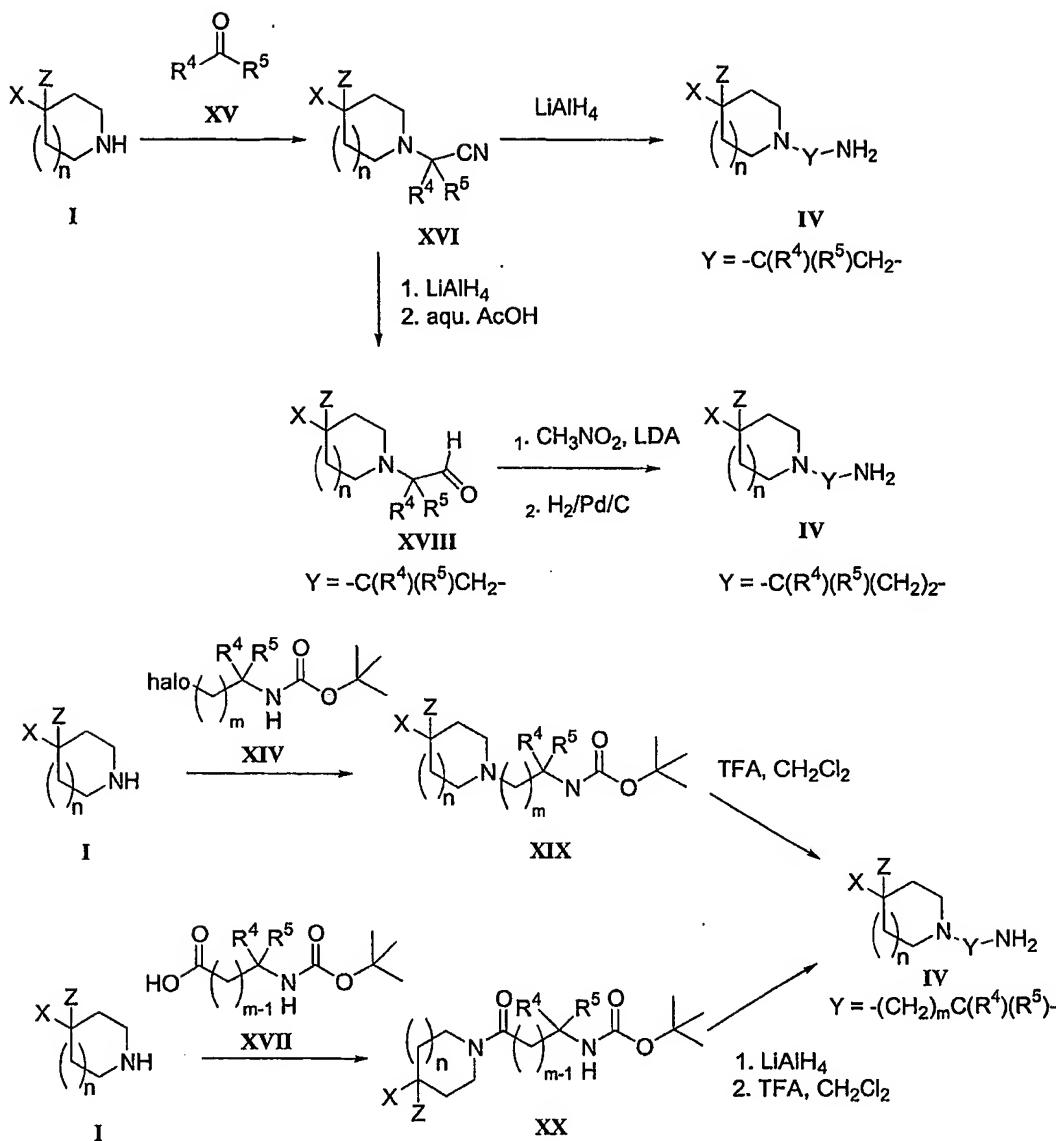


Reaction of amines of general structure X with isocyanates of general structure V provide symmetrical ureas of general structure VI. Reaction of amines of general

- 5 structure X with commercially available 2- or 3-isocyanato-carboxylic acid esters of
general formula XII in a polar aprotic solvent such as tetrahydrofuran, followed by
hydrolysis of the ester in aqueous acid such as HCl, provides carboxylic acids of
general structure II. Alternatively, isocyanates of general structure V and ureas of
general structure VI react with amino acid esters of general structure XIII to
10 provide, after hydrolysis of the ester in aqueous acid such as HCl, carboxylic acids
of general structure II.

Synthetic intermediates of general structure IV are obtained by the methods illustrated in Scheme G.

Scheme G



4-Substituted-piperidines and 3-substituted-pyrrolidines of general structure I in Scheme A are either commercially available in racemic or optically active form or are prepared in racemic or optically active form by methods well known in the art.

- 5 Ketones and aldehydes of general formula XV are commercially available or are prepared by methods well-known in the art. Reaction of ketones and aldehydes of general formula XV with 4-substituted-piperidines and 3-substituted-pyrrolidines of general structure I in presence of a cyanide ion donor such as acetone cyanohydrine provides piperidine and pyrrolidine derivatives of general structure
- 10 XVI. Complete reduction of the cyano group with a reducing reagent such as

- LiAlH₄ in a polar aprotic solvent such as THF provides the intermediate primary amines of general structure IV, wherein Y is -C(R⁴)(R⁵)-CH₂- . Partial reduction of the cyano group of compounds of general structure XVI with a reducing reagent such as DIBAL-H, followed by aqueous hydrolysis provides aldehydes of general structure XVIII. Condensation with the nitromethane anion and subsequent reduction, for example by catalytic hydrogenation, provides the intermediate primary amines of general structure IV, wherein Y is -C(R⁴)(R⁵)(CH₂)₂- . Haloalkyl carbamates of general structure XIV in Scheme G are commercially available or are prepared by methods well-known in the art. N-Alkylation of piperidines and pyrrolidines of general structure I with haloalkyl carbamates of general structure XIV is accomplished in a polar solvent such as THF in the presence of a small stoichiometric excess of acid scavenger such as DIPEA to provide compounds of general structure XIX. Cleavage of the resulting carbamate with methods well known in the art, for example with TFA in a solvent such as CH₂Cl₂, provides the intermediate primary amine derivatives of general structure IV wherein Y is -(CH₂)_mC(R⁴)(R⁵)- . Protected amino acids of general structure XVII are commercially available or are prepared by methods well-known in the art. N-Acylation of piperidines and pyrrolidines of general structure IV with compounds of general structure XVII is accomplished under well-known conditions, for example in a polar solvent such as DMF in the presence of a small stoichiometric excess of a coupling agent such as a carbodiimide, to provide compounds of general structure XX. Reduction with a reagent such as LiAlH₄ and deprotection provides intermediate primary amines of general structure IV wherein Y is -(CH₂)_mC(R⁴)(R⁵)-.
- 25 The foregoing general description of the invention will now be further illustrated with a number of non-limiting examples.

EXAMPLES OF THE INVENTION

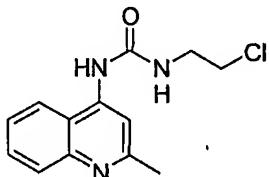
LIST OF ABBREVIATIONS:

| | |
|--------|-------------------------|
| BSA | bovine serum albumin |
| 30 CDI | N,N-carbonyldiimidazole |

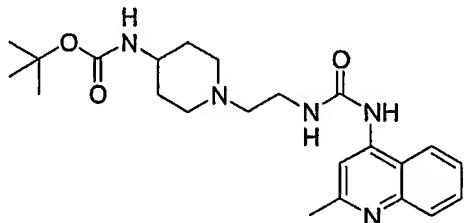
| | | |
|----|---------|--|
| | DIBAL-H | diisobutylaluminum hydride |
| | DIPEA | diisopropylethylamine |
| | DMF | dimethylformamide |
| | DMSO | dimethylsulfoxide |
| 5 | DPPA | diphenylphosphoryl azide |
| | EDC | N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride |
| | EDTA | ethylenediamine tetra-acetic acid |
| | ESI | electrospray ionization |
| | EtOAc | ethyl acetate |
| 10 | Hex | hexane |
| | HOBT | 1-hydroxybenzotriazole |
| | AcOH | acetic acid |
| | HPLC | high performance liquid chromatography |
| | LC-MS | liquid chromatography-mass spectroscopy |
| 15 | LDA | lithium diisopropylamide |
| | MeOH | methanol |
| | min | minutes |
| | MHz | megahertz |
| | MS | mass spectroscopy |
| 20 | NaHMDS | sodium bis(trimethylsilyl)amide |
| | NMR | nuclear magnetic resonance |

| | | |
|----|------------------|--|
| | ppm | part per million |
| | PBS | phosphate-buffered saline |
| | sat. | saturated |
| | T ₃ P | 1-propylphosphonic acid cyclic anhydride |
| 5 | TBTU | 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium bromide |
| | TEA | triethylamine |
| | TFA | trifluoroacetic acid |
| | THF | tetrahydrofuran |
| | TLC | thin layer chromatography |
| 10 | TMSCl | chlorotrimethylsilane |
| | t _R | retention time |

Reactions are routinely performed under an inert atmosphere such as N₂ gas in air dried glassware. Solvents are used as received from the vendor. Evaporations are performed in a rotary evaporator at reduced pressure and a water bath temperature of 50 °C. LC-MS characterizations are performed on a Finnigan HP1100 platform using ESI, and positive ion detection with a Navigator AQK detector. Analytical liquid chromatographic separations are performed by Method A, or where indicated, by Method B. Method A consists of a C18 column of 30 x 4.6 mm dimensions and a mobile phase consisting of a 1 minute gradient of 2 – 15 95% CH₃CN (containing 0.013 TFA) in water (containing 0.04% TFA) at a flow rate of 0.45 mL/min. Method B consists of a C18 column of 30 x 4.6 mm dimensions and an isocratic mobile phase consisting of CH₃CN-water (1:9) containing 1% formic acid. Retention time (t_R) is given in min. TLC is performed on pre-coated silica gel 60 F₂₅₄ glass-backed plates (Merck). Preparative HPLC is performed on 20 a Varian/Gilson platform using a C18 column of 60 x 21 mm dimensions and a mobile phase consisting of a gradient of 2 to 95% CH₃CN in water containing 0.05% formic acid. 25

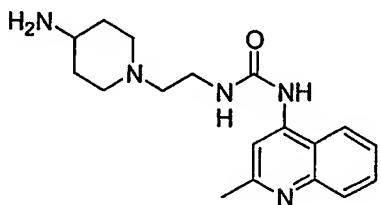
Example 1.**N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethyl-benzenesulfonamide****1A. 1-(2-Chloro-ethyl)-3-(2-methyl-quinolin-4-yl)-urea**

To a solution of 4-amino-2-methylquinoline (12.6 g, 80 mmol) in THF (480 mL) is added 2-chloroethylisocyanate (10.2 mL, 120 mmol) at rt. The reaction mixture is stirred for 40 h at rt. MeOH (100 mL) is added, and stirring is continued an additional hour. The reaction mixture is evaporated and the residue is taken up in CH₂Cl₂. The organic layer is shaken with 1 N HCl (250 mL), and the resulting precipitate is collected by filtration. The solid is washed with CH₂Cl₂ (100 mL), saturated NaHCO₃ (2 x 100 mL), and with water (4 x 100 mL). The resulting solid is dried under HV at rt for 14 h to provide the title compound.

1B. (1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester

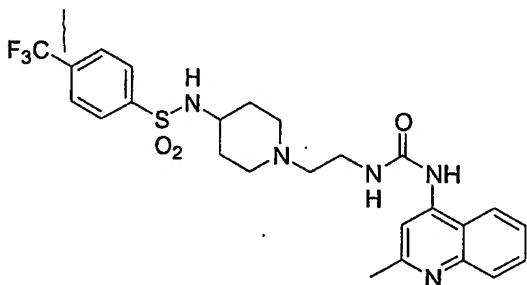
A mixture of piperidin-4-yl-carbamic acid tert-butyl ester (10 mmol), 1-(2-chloroethyl)-3-(2-methyl-quinolin-4-yl)-urea (10 mmol), NaHCO₃ (20 mmol), NaI (0.5 mmol), and THF (70 mL) is stirred in a sealed vessel at 70 °C for 6 d. The reaction mixture is filtered, evaporated to dryness, and the residue is purified by preparative HPLC to provide the title compound.

1C. 1-[2-(4-Amino-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea



A solution of (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester (2.86 g, 5.5 mmol) in AcOH (35 mL) is treated with conc. HCl (3.5 mL). After 30 min, the reaction mixture is frozen and lyophilized to provide the title compound as the dihydrochloride salt.

1D. N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethyl-benzenesulfonamide



10 A solution of 4-trifluoromethyl-benzenesulfonyl chloride (0.03 mmol) in THF (1 mL) is added to a mixture of 1-[2-(4-amino-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea (0.025 mmol), DIPEA (6 μ L) and THF (1 mL). The reaction mixture is heated at 40 °C for 18 h, and then is evaporated to dryness. The residue is taken up in formic acid (1 mL), and purified by preparative HPLC to provide the title compound.

15

The following compounds are prepared analogously:

| | Example | t _r | MS (ES+) |
|----|---|----------------|-------------|
| 1. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethyl-benzenesulfonamide | 1.04 | 536.2 |

| | | | |
|-----|--|------|-------|
| 2. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.91 | 454.2 |
| 3. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.98 | 468.2 |
| 4. | Thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 0.89 | 474.2 |
| 5. | Thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.89 | 460.2 |
| 6. | Thiophene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.97 | 474.2 |
| 7. | 3-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.00 | 482.2 |
| 8. | 3-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.00 | 468.2 |
| 9. | 3,N-Dimethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.06 | 482.2 |
| 10. | 2-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.99 | 482.2 |
| 11. | 2-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.99 | 468.2 |
| 12. | 2,N-Dimethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.05 | 482.2 |
| 13. | 4-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.00 | 482.2 |
| 14. | 4-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.99 | 468.2 |

| | | | |
|-----|--|------|-------|
| | ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | | |
| 15. | 4,N-Dimethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.06 | 482.2 |
| 16. | 2-Fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.92 | 486.2 |
| 17. | 2-Fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.93 | 472.2 |
| 18. | 2-Fluoro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.00 | 486.2 |
| 19. | 3-Fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.98 | 486.2 |
| 20. | 3-Fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.97 | 472.2 |
| 21. | 3-Fluoro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.04 | 486.2 |
| 22. | 4-Fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.97 | 486.2 |
| 23. | 4-Fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.97 | 472.2 |
| 24. | 4-Fluoro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.03 | 486.2 |
| 25. | 2-Cyano-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.93 | 493.2 |
| 26. | 2-Cyano-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.88 | 479.2 |

| | | | |
|-----|---|------|-------|
| 27. | 2-Cyano-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.99 | 493.2 |
| 28. | 3-Cyano-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.95 | 493.2 |
| 29. | 3-Cyano-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.95 | 479.2 |
| 30. | 3-Cyano-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.02 | 493.2 |
| 31. | 4-Cyano-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.96 | 493.2 |
| 32. | 4-Cyano-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.96 | 479.2 |
| 33. | 4-Cyano-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.02 | 493.2 |
| 34. | 3-Methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.99 | 498.2 |
| 35. | 3-Methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.99 | 484.2 |
| 36. | 3-Methoxy-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.04 | 498.2 |
| 37. | 4-Methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.97 | 498.2 |
| 38. | 4-Methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.97 | 484.2 |
| 39. | 4-Methoxy-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.03 | 498.2 |

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| | yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | | |
| 40. | 3-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.06 | 502.2 |
| 41. | 3-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.05 | 488.2 |
| 42. | 3-Chloro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.10 | 502.2 |
| 43. | 4-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.06 | 502.1 |
| 44. | 4-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.06 | 488.2 |
| 45. | 2-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.98 | 502.2 |
| 46. | 2-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.97 | 488.2 |
| 47. | 1-Methyl-1H-imidazole-4-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 0.62 | 472.2 |
| 48. | 1-Methyl-1H-imidazole-4-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.62 | 458.2 |
| 49. | 1-Methyl-1H-imidazole-4-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.67 | 472.2 |
| 50. | 3,4-Difluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.93 | 504.2 |

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| | ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | | |
| 51. | 3,4-Difluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.91 | 490.2 |
| 52. | 3,4-Difluoro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.98 | 504.2 |
| 53. | Biphenyl-4-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 1.06 | 544.2 |
| 54. | Biphenyl-4-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.06 | 530.2 |
| 55. | Biphenyl-4-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.08 | 544.2 |
| 56. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-propyl-benzenesulfonamide | 1.05 | 510.2 |
| 57. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-propyl-benzenesulfonamide | 1.04 | 496.2 |
| 58. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-propyl-benzenesulfonamide | 1.08 | 510.2 |
| 59. | 3-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-ylsulfamoyl)-benzoic acid | 0.60 | 512.2 |
| 60. | 3-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-ylsulfamoyl)-benzoic acid | 0.60 | 498.2 |
| 61. | 3-[Methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-sulfamoyl]-benzoic acid | 0.60 | 512.2 |
| 62. | Naphthalene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 1.03 | 518.2 |

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| 63. | Naphthalene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.02 | 504.2 |
| 64. | Naphthalene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.04 | 518.2 |
| 65. | Naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 1.00 | 518.2 |
| 66. | Naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.99 | 504.2 |
| 67. | Naphthalene-1-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.04 | 518.2 |
| 68. | Quinoline-8-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 0.87 | 519.2 |
| 69. | Quinoline-8-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.85 | 505.2 |
| 70. | Quinoline-8-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.87 | 519.2 |
| 71. | 4-tert-Butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.07 | 524.2 |
| 72. | 4-tert-Butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.07 | 510.2 |
| 73. | 4-tert-Butyl-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.09 | 524.2 |
| 74. | N-[4-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)sulfamoyl]-phenylacetamide | 0.76 | 525.2 |

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| | piperidin-4-ylsulfamoyl)-phenyl]-acetamide | | |
| 75. | N-[4-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-ylsulfamoyl)-phenyl]-acetamide | 0.76 | 511.2 |
| 76. | N-[4-[Methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-sulfamoyl]-phenyl]-acetamide | 0.81 | 525.2 |
| 77. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethyl-benzenesulfonamide | 1.03 | 522.2 |
| 78. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethyl-benzenesulfonamide | 1.06 | 536.2 |
| 79. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-trifluoromethyl-benzenesulfonamide | 0.97 | 536.2 |
| 80. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-trifluoromethyl-benzenesulfonamide | 0.95 | 522.1 |
| 81. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-trifluoromethyl-benzenesulfonamide | 1.02 | 536.2 |
| 82. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-trifluoromethyl-benzenesulfonamide | 1.03 | 536.2 |
| 83. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-3-trifluoromethyl-benzenesulfonamide | 1.02 | 522.2 |
| 84. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-3-trifluoromethyl-benzenesulfonamide | 1.05 | 536.2 |
| 85. | 3,4-Dichloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.05 | 536.1 |

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| | ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | | |
| 86. | 3,4-Dichloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.04 | 522.1 |
| 87. | 3,4-Dichloro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.07 | 536.1 |
| 88. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-pentyl-benzenesulfonamide | 1.11 | 538.3 |
| 89. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-pentyl-benzenesulfonamide | 1.10 | 524.2 |
| 90. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-pentyl-benzenesulfonamide | 1.12 | 538.3 |
| 91. | 4-Butoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.08 | 540.2 |
| 92. | 4-Butoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.08 | 526.2 |
| 93. | 4-Butoxy-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.09 | 540.2 |
| 94. | 4,5-Dichloro-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 1.05 | 542.1 |
| 95. | 4,5-Dichloro-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.04 | 528.0 |
| 96. | 4,5-Dichloro-thiophene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3- | 1.06 | 542.0 |

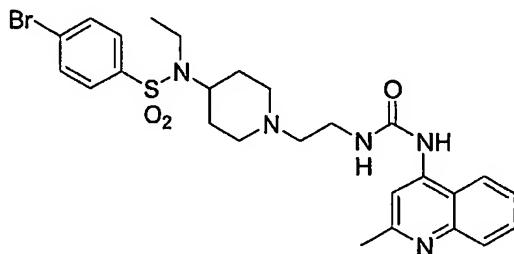
| | | | |
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| | yl)-amide | | |
| 97. | 4-(3-Chloro-2-cyano-phenoxy)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.08 | 619.2 |
| 98. | 4-(3-Chloro-2-cyano-phenoxy)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.08 | 605.2 |
| 99. | 4-(3-Chloro-2-cyano-phenoxy)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.09 | 619.2 |
| 100. | 2-Methanesulfonyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.86 | 546.2 |
| 101. | 2-Methanesulfonyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.83 | 532.1 |
| 102. | 2-Methanesulfonyl-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.83 | 546.1 |
| 103. | N-[4-Methyl-5-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)sulfamoyl]-thiazol-2-yl]-acetamide | 0.79 | 546.2 |
| 104. | N-[4-Methyl-5-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)sulfamoyl]-thiazol-2-yl]-acetamide | 0.79 | 532.2 |
| 105. | N-{4-Methyl-5-[methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)sulfamoyl]-thiazol-2-yl}-acetamide | 0.85 | 546.2 |

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| 106. | 3-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.98 | 546.1 |
| 107. | 3-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.96 | 532.0 |
| 108. | 3-Bromo-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.02 | 546.0 |
| 109. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.98 | 546.1 |
| 110. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.97 | 532.0 |
| 111. | 4-Bromo-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.03 | 546.1 |
| 112. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-trifluoromethoxy-benzenesulfonamide | 1.00 | 552.1 |
| 113. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-trifluoromethoxy-benzenesulfonamide | 0.99 | 538.1 |
| 114. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-trifluoromethoxy-benzenesulfonamide | 1.04 | 552.2 |
| 115. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethoxy-benzenesulfonamide | 1.05 | 552.1 |
| 116. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethoxy- | 1.04 | 538.1 |

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| | benzenesulfonamide | | |
| 117. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethoxy-benzenesulfonamide | 1.06 | 552.1 |
| 118. | 5-Dimethylamino-naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 0.94 | 561.2 |
| 119. | 5-Dimethylamino-naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.97 | 547.2 |
| 120. | 5-Dimethylamino-naphthalene-1-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.04 | 561.2 |
| 121. | 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 1.09 | 572.2 |
| 122. | 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.09 | 558.1 |
| 123. | 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.10 | 572.1 |
| 124. | 4-Bromo-2-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.07 | 574.1 |
| 125. | 4-Bromo-2-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.06 | 560.1 |

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| 126. | 4-Bromo-2-ethyl-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.09 | 574.1 |
| 127. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3,5-bis-trifluoromethyl-benzenesulfonamide | 1.09 | 604.1 |
| 128. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-3,5-bis-trifluoromethyl-benzenesulfonamide | 1.09 | 590.1 |
| 129. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-3,5-bis-trifluoromethyl-benzenesulfonamide | 1.10 | 604.2 |
| 130. | N-[5-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-ylsulfamoyl)-thiophen-2-ylmethyl]-benzamide | 0.96 | 607.2 |
| 131. | N-[5-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-ylsulfamoyl)-thiophen-2-ylmethyl]-benzamide | 0.94 | 593.1 |
| 132. | N-{5-[Methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-sulfamoyl]-thiophen-2-ylmethyl}-benzamide | 0.99 | 607.2 |
| 133. | 4-Benzenesulfonyl-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 1.04 | 614.1 |
| 134. | 4-Benzenesulfonyl-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.03 | 600.1 |

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| 135. | 4-Benzenesulfonyl-thiophene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.05 | 614.1 |
| 136. | 2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 1.03 | 619.2 |
| 137. | 2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.03 | 605.1 |
| 138. | 2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 1.05 | 619.2 |
| 139. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-C-phenyl-methanesulfonamide | 0.73 | 482.2 |
| 140. | Octane-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 1.05 | 504.3 |
| 141. | 2-Phenyl-ethanesulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 0.87 | 496.2 |
| 142. | 4-Chloro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.01 | 502.1 |

Example 143.4-Bromo-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide.

- 5 To a solution of 4-bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide (Example 109., 27.3 mg, 0.05 mmol) in DMSO (1 mL) are added ethyliodide (7.8 mg, 0.05 mmol) and CsCO₃ (40 mg, 12 mmol). The reaction mixture is stirred at room temperature for 3 h and then quenched with formic acid (0.25 mL). The reaction mixture is purified by preparative HPLC to provide the title compound.
- 10

The following compounds are prepared analogously:

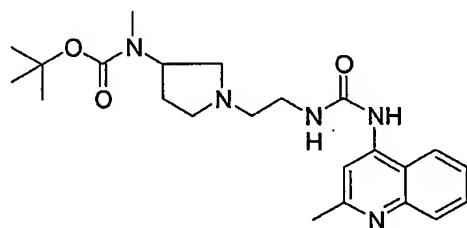
| | Example | t _r | MS (ES+) |
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| 143. | 4-Bromo-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.06 | 574.03 |
| 144. | 4-Bromo-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.05 | 559.99 |
| 145. | 4-Bromo-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.05 | 559.99 |
| 146. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-N-propyl-benzenesulfonamide | 1.09 | 588.06 |
| 147. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-N-propyl-benzenesulfonamide | 1.07 | 574.02 |

| | | | |
|-------------|---|------|--------|
| 148. | 4-Bromo-N-isobutyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.11 | 602.02 |
| 149. | 4-Bromo-N-isobutyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.09 | 588.03 |
| 150. | 4-Bromo-N-butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.1 | 602.06 |
| 151. | 4-Bromo-N-butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.09 | 588.04 |
| 152. | N-Benzyl-4-bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.11 | 636.03 |
| 153. | N-Benzyl-4-bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 1.1 | 622 |
| 154. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-N-phenethyl-benzenesulfonamide | 1.13 | 650.02 |
| 155. | 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-N-phenethyl-benzenesulfonamide | 1.11 | 636.02 |
| 156. | 4-Bromo-N-methyl-N-((R)-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.80 | 545.71 |
| 157. | 4-Bromo-N-ethyl-N-((R)-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.79 | 559.97 |
| 158. | 4-Bromo-N-ethyl-N-((S)-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.84 | 560.02 |

| | | | |
|------|---|------|--------|
| 159. | 4-Bromo-N-methyl-N-((S)-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide | 0.80 | 546.00 |
| 160. | N-Ethyl-3-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.98 | 510.40 |
| 161. | N-Ethyl-4-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.97 | 510.40 |
| 162. | N-Ethyl-2-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.97 | 510.40 |
| 163. | 3-Chloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.00 | 530.36 |
| 164. | 2-Chloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.97 | 530.36 |
| 165. | 4-Chloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.00 | 530.36 |
| 166. | N-Ethyl-4-fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.95 | 514.38 |
| 167. | N-Ethyl-4-methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 0.95 | 526.41 |
| 168. | 3,4-Dichloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide | 1.08 | 564.30 |
| 169. | N-Ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethyl-benzenesulfonamide | 1.07 | 564.36 |

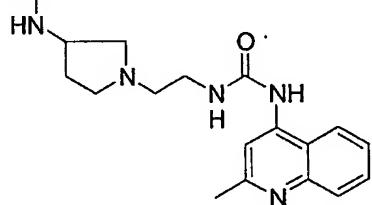
Example 170.**1-{2-[3-(3-Biphenyl-2-yl-1-methyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea****170A. Methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-**

5 carbamic acid tert-butyl ester



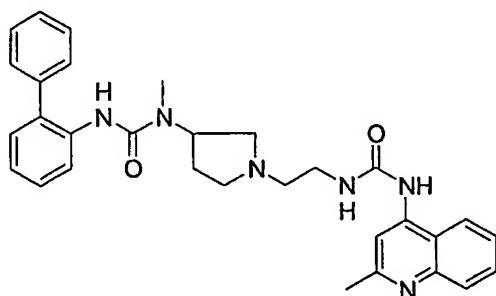
A mixture of methyl-pyrrolidin-3-yl-carbamic acid tert-butyl ester (10 mmol), 1-(2-chloro-ethyl)-3-(2-methyl-quinolin-4-yl)-urea (10 mmol), NaHCO₃ (20 mmol), NaI (0.5 mmol), and THF (70 mL) is stirred in a sealed vessel at 70 °C for 6 d. The

10 reaction mixture is filtered, evaporated to dryness, and the residue is purified by preparative HPLC to provide the title compound.

170B. 1-[2-(3-Methylamino-pyrrolidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

A solution of methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester (2.35 g, 5.5 mmol) in AcOH (35 mL) is treated with conc. HCl (3.5 mL). After 30 min, the reaction mixture is frozen and lyophilized to provide the title compound as the dihydrochloride salt.

170C. 1-{2-[3-(3-Biphenyl-2-yl-1-methyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea



- To a solution of 1-[2-(3-methylamino-pyrrolidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea (0.03 mmol) in THF (0.3 mL) is added a solution of 2-biphenyl isocyanate (0.09 mmol) in THF (0.6 mL). The reaction is allowed to stir for 18 h, and then is quenched with water (0.1 mL), and stirred for an additional 0.5 h. The reaction mixture is evaporated. The residue is taken up in a mixture of formic acid / TFA (1:1; 1 mL), and purified by preparative HPLC.
- 10 The following compounds are prepared analogously:

| | Example | t _r | MS (ES+) |
|------|---|----------------|-------------|
| 170. | 1-{2-[3-(3-Biphenyl-2-yl-1-methyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.93 | 523.3 |
| 171. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[4-(3-p-tolyl-ureido)-piperidin-1-yl]-ethyl}-urea | 0.91 | 461.2 |
| 172. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[3-(3-p-tolyl-ureido)-pyrrolidin-1-yl]-ethyl}-urea | 0.82 | 447.2 |
| 173. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[3-(1-methyl-3-p-tolyl-ureido)-pyrrolidin-1-yl]-ethyl}-urea | 0.82 | 461.2 |
| 174. | 1-{2-[4-(3-Biphenyl-2-yl-ureido)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 1.03 | 523.3 |

| | | | |
|------|--|------|-------|
| 175. | 1-{2-[3-(3-Biphenyl-2-yl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.97 | 509.2 |
| 176. | 1-(2-Methyl-quinolin-4-yl)-3-(2-{4-[3-(4-phenoxy-phenyl)-ureido]-piperidin-1-yl}-ethyl)-urea | 1.08 | 539.2 |
| 177. | 1-(2-Methyl-quinolin-4-yl)-3-(2-{3-[3-(4-phenoxy-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-urea | 1.04 | 525.2 |
| 178. | 1-(2-{3-[1-Methyl-3-(4-phenoxy-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 1.03 | 539.3 |
| 179. | 1-(2-{4-[3-(4-Ethyl-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.98 | 475.3 |
| 180. | 1-(2-{3-[3-(4-Ethyl-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.91 | 461.3 |
| 181. | 1-(2-{3-[3-(4-Ethyl-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.92 | 475.3 |
| 182. | 1-{2-[4-(3-Allyl-ureido)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.66 | 411.2 |
| 183. | 1-{2-[3-(3-Allyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.66 | 397.2 |
| 184. | 1-{2-[3-(3-Allyl-1-methyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.69 | 411.2 |
| 185. | 1-{2-[4-(3-Cyclohexyl-ureido)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.84 | 453.2 |
| 186. | 1-{2-[3-(3-Cyclohexyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.83 | 439.2 |
| 187. | 1-{2-[3-(3-Cyclohexyl-1-methyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.84 | 453.3 |

| | | | |
|------|--|------|-------|
| | ethyl}-3-(2-methyl-quinolin-4-yl)-urea | | |
| 188. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[4-(3-m-tolyl-ureido)-piperidin-1-yl]-ethyl}-urea | 0.90 | 461.3 |
| 189. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[3-(3-m-tolyl-ureido)-pyrrolidin-1-yl]-ethyl}-urea | 0.82 | 447.2 |
| 190. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[3-(1-methyl-3-m-tolyl-ureido)-pyrrolidin-1-yl]-ethyl}-urea | 0.83 | 461.2 |
| 191. | 1-(2-{4-[3-(4-Methoxy-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.81 | 477.3 |
| 192. | 1-(2-{3-[3-(4-Methoxy-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.76 | 463.2 |
| 193. | 1-(2-{3-[3-(4-Methoxy-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.76 | 477.2 |
| 194. | 1-(2-{4-[3-(2-Methoxy-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.87 | 477.3 |
| 195. | 1-(2-{3-[3-(2-Methoxy-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.81 | 463.2 |
| 196. | 1-(2-{3-[3-(2-Methoxy-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.82 | 477.2 |
| 197. | 1-{2-[4-(3-Ethyl-ureido)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.64 | 399.2 |
| 198. | 1-{2-[3-(3-Ethyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.63 | 385.2 |
| 199. | 1-{2-[3-(3-Ethyl-1-methyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.66 | 399.2 |

| | | | |
|-------------|---|------|-------|
| 200. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[4-(3-o-tolyl-ureido)-piperidin-1-yl]-ethyl}-urea | 0.83 | 461.2 |
| 201. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[3-(3-o-tolyl-ureido)-pyrrolidin-1-yl]-ethyl}-urea | 0.81 | 447.2 |
| 202. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[3-(1-methyl-3-o-tolyl-ureido)-pyrrolidin-1-yl]-ethyl}-urea | 0.79 | 461.2 |
| 203. | 1-(2-{4-[3-(3-Chloro-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.97 | 481.2 |
| 204. | 1-(2-{3-[3-(3-Chloro-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.87 | 467.2 |
| 205. | 1-(2-{3-[3-(3-Chloro-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.87 | 481.2 |
| 206. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[4-(3-naphthalen-2-yl-ureido)-piperidin-1-yl]-ethyl}-urea | 1.02 | 497.3 |
| 207. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[3-(3-naphthalen-2-yl-ureido)-pyrrolidin-1-yl]-ethyl}-urea | 0.89 | 483.2 |
| 208. | 1-{2-[3-(1-Methyl-3-naphthalen-2-yl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.89 | 497.2 |
| 209. | 1-(2-{4-[3-(2,4-Difluoro-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.87 | 483.2 |
| 210. | 1-(2-{3-[3-(2,4-Difluoro-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.81 | 469.2 |
| 211. | 1-(2-{3-[3-(2,4-Difluoro-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.79 | 483.2 |
| 212. | 1-{2-[4-(3-Butyl-ureido)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.76 | 427.3 |

| | | | |
|------|---|------|-------|
| | methyl-quinolin-4-yl)-urea | | |
| 213. | 1-{2-[3-(3-Butyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.75 | 413.2 |
| 214. | 1-{2-[3-(3-Butyl-1-methyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.78 | 427.2 |
| 215. | 1-{2-[4-(3-Benzyl-ureido)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.82 | 461.2 |
| 216. | 1-{2-[3-(3-Benzyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.80 | 447.2 |
| 217. | 1-{2-[3-(3-Benzyl-1-methyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.79 | 461.2 |
| 218. | 1-(2-[4-[3-(2-Fluoro-phenyl)-ureido]-piperidin-1-yl]-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.85 | 465.2 |
| 219. | 1-(2-[3-[3-(2-Fluoro-phenyl)-ureido]-pyrrolidin-1-yl]-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.79 | 451.2 |
| 220. | 1-(2-[3-[3-(2-Fluoro-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl]-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.76 | 465.2 |
| 221. | 1-(2-[4-[3-(4-Fluoro-phenyl)-ureido]-piperidin-1-yl]-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.87 | 465.2 |
| 222. | 1-(2-[3-[3-(4-Fluoro-phenyl)-ureido]-pyrrolidin-1-yl]-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.80 | 451.2 |
| 223. | 1-(2-[3-[3-(4-Fluoro-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl]-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.80 | 465.2 |
| 224. | 1-(2-[4-[3-(3-Fluoro-phenyl)-ureido]-piperidin-1-yl]-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.90 | 465.2 |

| | | | |
|-------------|--|------|-------|
| 225. | 1-(2-{3-[3-(3-Fluoro-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.81 | 451.1 |
| 226. | 1-(2-{3-[3-(3-Fluoro-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.81 | 465.2 |
| 227. | 1-(2-{4-[3-(2-Methyl-benzyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.89 | 475.2 |
| 228. | 1-(2-{3-[3-(2-Methyl-benzyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.85 | 461.2 |
| 229. | 1-(2-{3-[1-Methyl-3-(2-methyl-benzyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.85 | 475.2 |
| 230. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[4-(3-phenethyl-ureido)-piperidin-1-yl]-ethyl}-urea | 0.88 | 475.2 |
| 231. | 1-(2-Methyl-quinolin-4-yl)-3-{2-[3-(3-phenethyl-ureido)-pyrrolidin-1-yl]-ethyl}-urea | 0.85 | 461.2 |
| 232. | 1-{2-[3-(1-Methyl-3-phenethyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.86 | 475.2 |
| 233. | 1-(2-{4-[3-(3-Methoxy-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.86 | 477.3 |
| 234. | 1-(2-{3-[3-(3-Methoxy-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.77 | 463.2 |
| 235. | 1-(2-{3-[3-(3-Methoxy-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.78 | 477.2 |
| 236. | 1-(2-{4-[3-(4-Fluoro-benzyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.87 | 479.2 |
| 237. | 1-(2-{3-[3-(4-Fluoro-benzyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.82 | 465.2 |

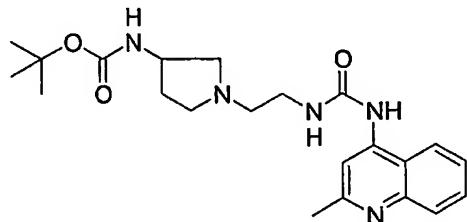
| | | | |
|------|--|------|-------|
| | ethyl)-3-(2-methyl-quinolin-4-yl)-urea | | |
| 238. | 1-(2-{3-[3-(4-Fluoro-benzyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.82 | 479.2 |
| 239. | 1-(2-{4-[3-(2-Isopropyl-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.98 | 489.2 |
| 240. | 1-(2-{3-[3-(2-Isopropyl-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.95 | 475.3 |
| 241. | 1-(2-{3-[3-(2-Isopropyl-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.93 | 489.3 |
| 242. | 1-(2-{4-[3-(4-Isopropyl-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 1.05 | 489.2 |
| 243. | 1-(2-{3-[3-(4-Isopropyl-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 1.00 | 475.2 |
| 244. | 1-(2-{3-[3-(4-Isopropyl-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.99 | 489.3 |
| 245. | 1-(2-{4-[3-(4-Bromo-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 1.00 | 525.1 |
| 246. | 1-(2-{3-[3-(4-Bromo-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.89 | 511.1 |
| 247. | 1-(2-{3-[3-(4-Bromo-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.88 | 525.1 |
| 248. | 1-(2-Methyl-quinolin-4-yl)-3-(2-{4-[3-(2-phenoxy-phenyl)-ureido]-piperidin-1-yl}-ethyl)-urea | 1.07 | 539.2 |
| 249. | 1-(2-Methyl-quinolin-4-yl)-3-(2-{3-[3-(2-phenoxy-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-urea | 1.04 | 525.2 |

| | | | |
|------|--|------|-------|
| 250. | 1-(2-{3-[1-Methyl-3-(2-phenoxy-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 1.03 | 539.2 |
| 251. | 1-{2-[4-(3-tert-Butyl-ureido)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.76 | 427.2 |
| 252. | 1-{2-[3-(3-tert-Butyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.75 | 413.2 |
| 253. | 1-{2-[3-(3-tert-Butyl-1-methyl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.79 | 427.2 |
| 254. | 1-(2-{4-[3-(4-Chloro-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.98 | 481.1 |
| 255. | 1-(2-{3-[3-(4-Chloro-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.87 | 467.2 |
| 256. | 1-(2-{3-[3-(4-Chloro-phenyl)-1-methyl-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea | 0.86 | 481.2 |

Example 257.

Pyridine-2-carboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide

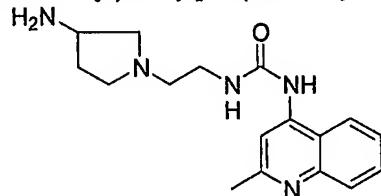
- 5 257A. (1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester



A mixture of pyrrolidin-3-yl-carbamic acid tert-butyl ester (10 mmol), 1-(2-chloroethyl)-3-(2-methyl-quinolin-4-yl)-urea (10 mmol), NaHCO₃ (20 mmol), NaI (0.5

mmol), and THF (70 mL) is stirred in a sealed vessel at 70 °C for 6 d. The reaction mixture is filtered, evaporated to dryness, and the residue is purified by preparative HPLC to provide the title compound.

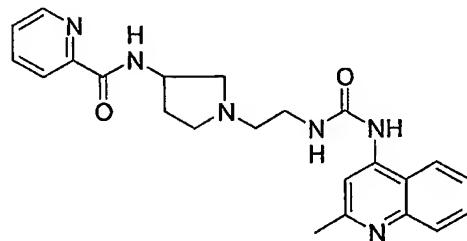
257B. 1-[2-(3-Amino-pyrrolidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea



5

A solution of (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester (5.5 mmol) in AcOH (35 mL) is treated with conc. HCl (3.5 mL). After 30 min, the reaction mixture is frozen and lyophilized to provide the title compound as the dihydrochloride salt.

- 10 **257C. Pyridine-2-carboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide**



- To a solution of 1-[2-(3-amino-pyrrolidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea (0.03 mmol) in DMF (0.3 mL) is added DIPEA (3 eq). The resulting solution is
15 treated with a solution of pyridine-2-carboxylic acid (1.1 eq) in DMF (0.25 mL). A solution of TBTU (1.1 eq) in DMF (0.25 mL) is added. The reaction is stirred at 20 C for 45 min. The reaction mixture is evaporated to dryness. The residue is taken up in CH3CN/H2O/TFA (6:10:1; 1 mL) and is purified by preparative HPLC.

The following compounds are prepared analogously:

| | Example | t _r | MS (ES+) |
|------|---|----------------|-------------|
| 257. | Pyridine-2-carboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.70 | 419.2 |
| 258. | 2-(4-Chloro-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide | 0.92 | 480.2 |
| 259. | 2-(4-Chloro-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.91 | 466.2 |
| 260. | 2-(4-Chloro-phenyl)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.92 | 480.2 |
| 261. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-nicotinamide | 0.62 | 433.2 |
| 262. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-nicotinamide | 0.61 | 419.2 |
| 263. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-nicotinamide | 0.61 | 433.2 |
| 264. | Pyridine-2-carboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 0.73 | 433.2 |
| 265. | Pyridine-2-carboxylic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.66 | 433.2 |
| 266. | 2-(4-Methoxy-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide | 0.82 | 476.2 |
| 267. | 2-(4-Methoxy-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.81 | 462.2 |
| 268. | 2-(4-Methoxy-phenyl)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.84 | 476.2 |

| | | | |
|------|---|------|-------|
| 269. | Naphthalene-2-carboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 0.98 | 482.2 |
| 270. | Naphthalene-2-carboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.89 | 468.2 |
| 271. | Naphthalene-2-carboxylic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.89 | 482.3 |
| 272. | 2-(4-Isopropyl-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide | 1.05 | 488.3 |
| 273. | 2-(4-Isopropyl-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 1.04 | 474.3 |
| 274. | 2-(4-Isopropyl-phenyl)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 1.05 | 488.3 |
| 275. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-naphthalen-1-yl-acetamide | 0.98 | 496.2 |
| 276. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-naphthalen-1-yl-acetamide | 0.94 | 482.2 |
| 277. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-naphthalen-1-yl-acetamide | 0.95 | 496.2 |
| 278. | Cyclopentanecarboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 0.77 | 424.2 |
| 279. | Cyclopentanecarboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.76 | 410.2 |
| 280. | Cyclopentanecarboxylic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)- | 0.82 | 424.2 |

| | | | |
|------|---|------|-------|
| | amide | | |
| 281. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzamide | 0.78 | 432.2 |
| 282. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 0.76 | 418.2 |
| 283. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 0.77 | 432.2 |
| 284. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-o-tolyl-acetamide | 0.87 | 460.2 |
| 285. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-o-tolyl-acetamide | 0.85 | 446.2 |
| 286. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-o-tolyl-acetamide | 0.87 | 460.3 |
| 287. | 3-(4-Fluoro-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-propionamide | 0.89 | 478.2 |
| 288. | 3-(4-Fluoro-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-propionamide | 0.88 | 464.2 |
| 289. | 3-(4-Fluoro-phenyl)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-propionamide | 0.91 | 478.2 |
| 290. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-isonicotinamide | 0.61 | 433.2 |
| 291. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-isonicotinamide | 0.61 | 419.2 |
| 292. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-isonicotinamide | 0.59 | 433.2 |

| | | | |
|------|--|------|-------|
| | ethyl}-pyrrolidin-3-yl)-isonicotinamide | | |
| 293. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-phenyl-propionamide | 0.86 | 460.3 |
| 294. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-3-phenyl-propionamide | 0.84 | 446.2 |
| 295. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-3-phenyl-propionamide | 0.88 | 460.2 |
| 296. | 2-(4-Fluoro-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide | 0.83 | 464.2 |
| 297. | 2-(4-Fluoro-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.82 | 450.2 |
| 298. | 2-(4-Fluoro-phenyl)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.86 | 464.2 |
| 299. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-p-tolyl-propionamide | 0.94 | 474.3 |
| 300. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-3-p-tolyl-propionamide | 0.93 | 460.2 |
| 301. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-3-p-tolyl-propionamide | 0.97 | 474.3 |
| 302. | 3-(2-Methoxy-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-propionamide | 0.91 | 490.3 |
| 303. | 3-(2-Methoxy-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-propionamide | 0.88 | 476.3 |
| 304. | 3-(2-Methoxy-phenyl)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)- | 0.91 | 490.3 |

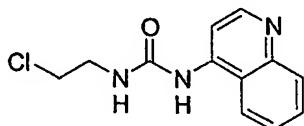
| | | | |
|------|--|------|-------|
| | propionamide | | |
| 305. | 3-(4-Methoxy-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-propionamide | 0.87 | 490.3 |
| 306. | 3-(4-Methoxy-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-propionamide | 0.86 | 476.3 |
| 307. | 3-(4-Methoxy-phenyl)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-propionamide | 0.89 | 490.3 |
| 308. | 3-(3-Methoxy-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-propionamide | 0.88 | 490.2 |
| 309. | 3-(3-Methoxy-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-propionamide | 0.87 | 476.2 |
| 310. | 3-(3-Methoxy-phenyl)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-propionamide | 0.89 | 490.2 |
| 311. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide | 0.80 | 446.2 |
| 312. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-phenyl-acetamide | 0.79 | 432.2 |
| 313. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-phenyl-acetamide | 0.82 | 446.2 |
| 314. | 4-Fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzamide | 0.83 | 450.2 |
| 315. | 4-Fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 0.80 | 436.2 |

| | | | |
|------|--|------|-------|
| 316. | 4-Fluoro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 0.78 | 450.2 |
| 317. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-m-tolyl-acetamide | 0.88 | 460.2 |
| 318. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-m-tolyl-acetamide | 0.87 | 446.2 |
| 319. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-m-tolyl-acetamide | 0.91 | 460.2 |
| 320. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-p-tolyl-acetamide | 0.89 | 460.2 |
| 321. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-p-tolyl-acetamide | 0.87 | 446.3 |
| 322. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-p-tolyl-acetamide | 0.91 | 460.2 |
| 323. | 3-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzamide | 0.91 | 466.1 |
| 324. | 3-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 0.85 | 452.1 |
| 325. | 3-Chloro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 0.84 | 466.2 |
| 326. | Quinoline-6-carboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 0.67 | 483.2 |
| 327. | Quinoline-6-carboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.66 | 469.2 |
| 328. | Quinoline-6-carboxylic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.63 | 483.2 |

| | | | |
|------|---|------|-------|
| | quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | | |
| 329. | 4-tert-Butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzamide | 1.06 | 488.3 |
| 330. | 4-tert-Butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 1.04 | 474.2 |
| 331. | 4-tert-Butyl-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 1.05 | 488.3 |
| 332. | 2-(4-Dimethylamino-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide | 0.64 | 489.3 |
| 333. | 2-(4-Dimethylamino-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.62 | 475.2 |
| 334. | 2-(4-Dimethylamino-phenyl)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.65 | 489.3 |
| 335. | 2,4-Dimethoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzamide | 0.89 | 492.2 |
| 336. | 2,4-Dimethoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 0.83 | 478.2 |
| 337. | 2,4-Dimethoxy-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 0.81 | 492.2 |
| 338. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-pyrrol-1-yl-benzamide | 1.00 | 497.2 |
| 339. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-pyrrol-1-yl-benzamide | 0.95 | 483.2 |
| 340. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-pyrrol-1-yl-benzamide | 0.95 | 497.2 |

| | | | |
|------|---|------|-------|
| | ethyl}-pyrrolidin-3-yl)-4-pyrrol-1-yl-benzamide | | |
| 341. | 2-(4-Bromo-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide | 0.95 | 524.1 |
| 342. | 2-(4-Bromo-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.93 | 510.1 |
| 343. | 2-(4-Bromo-phenyl)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.94 | 524.1 |
| 344. | 4-Benzoyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzamide | 1.03 | 536.2 |
| 345. | 4-Benzoyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 0.99 | 522.2 |
| 346. | 4-Benzoyl-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide | 0.98 | 536.2 |
| 347. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide | 0.60 | 370.2 |
| 348. | N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.59 | 356.2 |
| 349. | N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-acetamide | 0.62 | 370.2 |
| 350. | 4-Methoxy-cyclohexanecarboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 0.74 | 468.3 |
| 351. | 4-Methoxy-cyclohexanecarboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide | 0.75 | 468.3 |

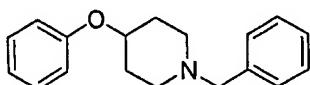
| | | | |
|------|---|------|-------|
| 352. | 1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.7 | 403.3 |
| 353. | 4-Methoxy-cyclohexanecarboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.72 | 454.2 |
| 354. | 4-Methoxy-cyclohexanecarboxylic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.75 | 454.2 |
| 355. | 4-Methoxy-cyclohexanecarboxylic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.73 | 468.2 |
| 356. | 4-Methoxy-cyclohexanecarboxylic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide | 0.78 | 468.3 |

Example 357.**1-[2-(4-Phenoxy-piperidin-1-yl)-ethyl]-3-quinolin-4-yl-urea****357A. 1-(2-Chloroethyl)-3-quinolin-4-yl-urea**

To a solution of 4-aminoquinoline (3.46 g, 24 mmol) in dry THF is added chloroethylisocyanate (3.1 mL, 36 mmol). The reaction mixture is stirred for 18 h. MeOH (10 mL) is added, and stirring is continued for an additional hour. The reaction mixture is evaporated, and partitioned between DCM and aqueous 5% citric acid (150 mL). The aqueous layer is carefully adjusted to pH 9 with solid

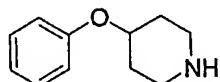
NaHCO_3 . The precipitate is filtered, washed with H_2O (5×20 mL) and Et_2O (2×20 mL), and dried in vacuo at 45°C to provide the title compound.

357B. 1-Benzyl-4-phenoxy-piperidine



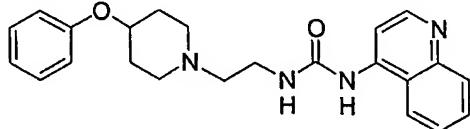
- 5 To a cold (0°C) mixture of phenol (190 mg, 2.02 mmol) and triphenylphosphine (680 mg, 2.6 mmol) in dry THF (6.4 mL) is added dropwise over 30 min a solution of 1-benzyl-piperidin-4-ol (490 mg, 2.6 mmol) and diethylazadicarboxylate (0.41 mL, 2.6 mmol) in dry THF (4.8 mL). The mixture is stirred at room temperature under nitrogen for 20 h. The mixture is dissolved in EtOAc , washed with sat.
- 10 NaHCO_3 (2×20 mL), dried (MgSO_4), filtered and concentrated to provide a crude oil. Flash chromatography (EtOAc/Hex : 3/7) provides the title compound.

357C. 4-Phenoxy-piperidine



- 15 A mixture of 1-benzyl-4-phenoxy-piperidine (420 mg, 1.6 mmol), Pd-C 10% (10 mg) and TFA (0.18 mL, 1.6 mmol) in MeOH (5 mL) is hydrogenated at room temperature and atmospheric pressure for 20 h. The mixture is filtered over Celite and the filtrate is concentrated under reduced pressure. The residue is dissolved in CH_2Cl_2 , washed with sat. NaHCO_3 , filtered and concentrated to provide the title compound.

20 357D. 1-[2-(4-Phenoxy-piperidin-1-yl)-ethyl]-3-quinolin-4-yl-urea



To a solution of 4-phenoxy-piperidine (0.03 mmol) in dry THF (1 mL) is added 1-(2-chloro-ethyl)-3-quinolin-4-yl-urea (0.03 mmol), solid NaHCO_3 (2.5 mg), and NaI

(1 mg). The flask is tightly sealed, and shaken at 70°C for 6 days. The reaction mixture is evaporated, taken up in aqueous formic acid, and purified by preparative HPLC to provide the title compound.

The following compounds are prepared in an analogous fashion. Values in
5 parentheses are obtained by analytical Method B as described in the Experimental
Section above.

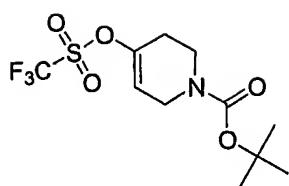
| | Example | t _r | MS (ES+) |
|------|--|----------------|-------------|
| 357. | 1-[2-(4-Phenoxy-piperidin-1-yl)-ethyl]-3-quinolin-4-yl-urea | (2.58) | 391 |
| 358. | 1-{2-[4-(2-Methoxy-phenoxy)-piperidin-1-yl]-ethyl}-3-quinolin-4-yl-urea | (2.66) | 421 |
| 359. | 1-Quinolin-4-yl-3-[2-(4-o-tolyloxy-piperidin-1-yl)-ethyl]-urea | (3.68) | 405 |
| 360. | 1-{2-[4-(2-Methoxy-phenoxy)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | (2.70) | 435 |
| 361. | 1-(2-Methyl-quinolin-4-yl)-3-[2-(4-phenoxy-piperidin-1-yl)-ethyl]-urea | (2.58) | 405 |
| 362. | 1-(2-Methyl-quinolin-4-yl)-3-[2-(4-o-tolyloxy-piperidin-1-yl)-ethyl]-urea | (3.65) | 419 |

Example 363.

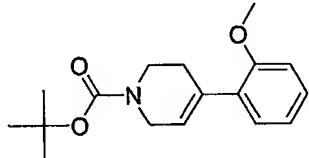
1-{2-[4-(2-Methoxy-phenyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-

10 urea

363A. 4-Trifluoromethanesulfonyl-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester

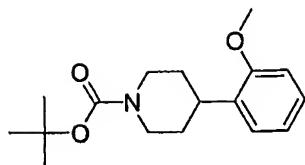


- To a cooled (-78°C) solution of LDA (2.76 mL, 5.52 mmol) in anhydrous THF (6 mL), is added dropwise a solution of 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (1 g, 5.02 mmol) in anhydrous THF (6 mL). After stirring at -78°C for 20 min,
- 5 a solution of *N*-phenyltrifluoromethanesulfonimide (1.91 g, 5.34 mmol) in anhydrous THF (6 mL) is added dropwise. The mixture is stirred at 0°C for 3 h and then concentrated in vacuo. The resulting oil is dissolved in CH₂Cl₂ (3 mL) and loaded onto a pad of neutral alumina and eluted with (Hex/EtOAc, 9/1) to provide the title compound.
- 10 **363B.** 4-(2-Methoxy-phenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester



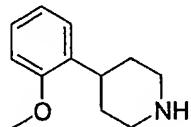
- A three necked flask purged with nitrogen is charged with aqueous 2N Na₂CO₃ (1.4 mL), 1,2-dimethoxyethane (3.7 mL), 2-methoxyphenyl boronic acid (206 mg, 1.35 mmol), anhydrous lithium chloride (123 mg, 2.9 mmol), 4-trifluoromethanesulfonyl-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (321 mg, 0.96 mmol) and tetrakis(triphenylphosphine)palladium (56 mg, 0.048 mmol). The mixture is stirred at reflux for 2 h under nitrogen, cooled and concentrated under reduced pressure. The residue is partitioned between CH₂Cl₂ (10 mL), aqueous 2N Na₂CO₃ (10 mL), and concentrated NH₄OH (1 mL). The aqueous layer is extracted twice with CH₂Cl₂. The combined organic layers are dried (MgSO₄), filtered and concentrated to provide a crude oil. Flash chromatography (Hex/ AcOEt/ CH₂Cl₂: 5/1/1) provides the title compound.

363C. 4-(2-Methoxy-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester



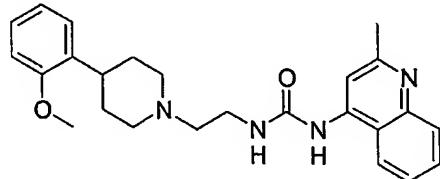
A mixture of 4-(2-methoxy-phenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (200 mg, 0.69 mmol), Pd-C 10% (30 mg) in EtOAc (5 mL) is hydrogenated at room temperature and atmospheric pressure for 20 h. The
5 mixture is filtered over Celite, and the filtrate is evaporated to provide the title compound.

363D. 4-(2-Methoxy-phenyl)-piperidine



A mixture of 4-(2-methoxy-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (190 mg, 0.65 mmol), and TFA (0.35 mL, 4.8 mmol) in dry CH₂Cl₂ (5 mL) is stirred at
10 room temperature under nitrogen for 2 h. The mixture is concentrated under reduced pressure, and the residue is combined with CH₂Cl₂/ sat. aqueous NaHCO₃. The aqueous layer is extracted twice with CH₂Cl₂, the combined organic extracts are washed with brine, dried (MgSO₄), filtered and concentrated to
15 provide the title compound.

363E. 1-{2-[4-(2-Methoxy-phenyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea



To a solution of 4-(2-methoxy-phenyl)-piperidine (0.03 mmol) in dry THF (1 mL) is
20 added 1-(2-chloro-ethyl)-3-quinolin-4-yl-urea (0.03 mmol), solid NaHCO₃ (2.5 mg), and NaI (1 mg). The flask is tightly sealed, and shaken at 70°C for 6 days. The

reaction mixture is evaporated, taken up in aqueous formic acid, and purified by preparative HPLC to provide the title compound.

The following compounds are prepared in an analogous fashion. Values in parentheses are obtained by analytical Method B as described in the Experimental

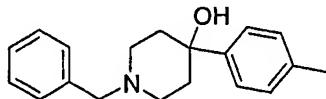
5 Section above.

| | Example | t _r | MS (ES+) |
|------|---|----------------|-------------|
| 363. | 1-[2-[4-(2-Methoxy-phenyl)-piperidin-1-yl]-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | (3.68) | 419 |
| 364. | 1-[2-(4-Phenyl-piperidin-1-yl)-ethyl]-3-quinolin-4-yl-urea | (3.49) | 375 |
| 365. | 1-(2-Methyl-quinolin-4-yl)-3-[2-(4-phenyl-piperidin-1-yl)-ethyl]-urea | (3.56) | 389 |
| 366. | 1-Quinolin-4-yl-3-[2-(4-o-tolyl-piperidin-1-yl)-ethyl]-urea | (3.63) | 389 |
| 367. | 1-(2-Methyl-quinolin-4-yl)-3-[2-(4-o-tolyl-piperidin-1-yl)-ethyl]-urea | (3.72) | 403 |

Example 368.

1-[2-(4-Hydroxy-4-p-tolyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

368A. 1-Benzyl-4-p-tolyl-piperidin-4-ol

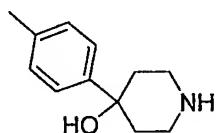


10

A solution of 4-bromotoluene (1.017 g, 5.94 mmol) in anhydrous Et₂O (6 mL), is added dropwise to a mixture of Mg (0.159 g, 6.54 mmol) and a catalytic amount of I₂ (0.015 g, 0.26 mmol) in anhydrous Et₂O (10 mL). The mixture is stirred at reflux

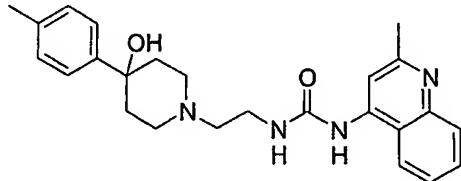
for 5 h under nitrogen. To this cloudy solution is added dropwise at 0°C, a solution of *N*-benzyl-4-piperidone (1.063 mL, 5.94 mmol) in anhydrous Et₂O (6 mL) and the mixture is stirred at reflux for 1.5 h. After cooling, the mixture is poured into sat. NH₄Cl (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts are washed with brine, dried (MgSO₄), filtered and concentrated to provide a crude oil. Flash chromatography (EtOAc/ Hex: 3/7) affords the title compound.

368B. 4-*p*-Tolyl-piperidin-4-ol



10 A mixture of 1-benzyl-4-*p*-tolyl-piperidin-4-ol (350 mg, 1.243 mmol), and Pd-C 10% (55 mg) in EtOAc (7 mL) is hydrogenated at room temperature and atmospheric pressure for 20 h. The mixture is filtered over Celite, and the filtrate is evaporated to provide the title compound.

368C. 1-[2-(4-Hydroxy-4-*p*-tolyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

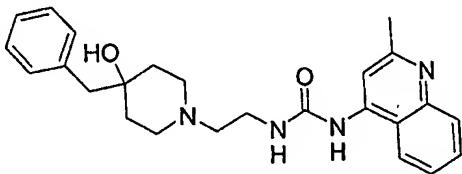


To a solution of 4-*p*-tolyl-piperidin-4-ol (0.03 mmol) in dry THF (1 mL) is added 1-(2-chloro-ethyl)-3-(2-methyl-quinolin-4-yl)-urea (0.03 mmol), solid NaHCO₃ (2.5 mg), and NaI (1 mg). The flask is tightly sealed, and shaken at 70°C for 6 days.

20 The reaction mixture is evaporated, taken up in aqueous formic acid, and purified by preparative HPLC to provide the title compound.

| | | | |
|--|---------|----------------|-------------|
| | Example | t _r | MS (ES+) |
|--|---------|----------------|-------------|

| | | | |
|------|--|------|-------|
| 368. | 1-[2-(4-Hydroxy-4-p-tolyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.95 | 419.5 |
|------|--|------|-------|

Example 369.**1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea**

- 5 To a solution of 4-hydroxy-4-benzyl-piperidine (380.6 mg, 2 mmol) in dry THF (10 mL) is added 1-(2-chloro-ethyl)-3-(2-methyl-quinolin-4-yl)-urea (263.7 mg, 1 mmol) and solid NaHCO₃ (672 mg, 8 mmol). The reaction mixture is stirred at 45°C for 6 days. The reaction mixture is diluted with CH₂Cl₂ (100 mL) and washed with sat. Na₂CO₃ (2x30 mL). The aqueous phase is re-extracted with CH₂Cl₂ (2x25 mL), the combined organic phases are washed with brine (20 mL), dried (Na₂SO₄), filtered and evaporated. The residue is purified by preparative HPLC to provide the title compound.
- 10
- 15

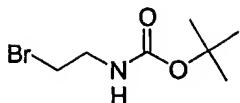
The following compounds are prepared in an analogous fashion. Values in parentheses are obtained by analytical Method B as described in the Experimental Section above.

| | Example | t _r | MS (ES+) |
|------|---|----------------|----------|
| 369. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.89 | 419.2 |
| 370. | 1-[2-(4-Hydroxy-4-phenyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 1.09 | 405.2 |
| 371. | 1-[2-[4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl]-3-quinolin-4-yl-urea | (2.54) | 425 |

| | | | |
|------|--|--------|-------|
| | ethyl}-3-quinolin-4-yl-urea | | |
| 372. | 1-[2-[4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | (2.79) | 439 |
| 373. | 1-[2-[4-(4-Bromo-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl}-3-quinolin-4-yl-urea | (2.68) | 470 |
| 374. | 1-[2-[4-(4-Bromo-phenyl)-4-hydroxy-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | (2.58) | 484 |
| 375. | 1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-quinolin-4-yl-urea | 1.02 | 389.2 |
| 376. | 1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.7 | 403.3 |
| 377. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-quinolin-4-yl-urea | 0.87 | 405.2 |
| 378. | 1-[2-[4-(Hydroxy-diphenyl-methyl)-piperidin-1-yl]-ethyl]-3-quinolin-4-yl-urea | 1.02 | 481.6 |
| 379. | 1-[2-(4-Benzoyl-piperidin-1-yl)-ethyl]-3-quinolin-4-yl-urea | (2.73) | 401.6 |
| 380. | 1-[2-(4-Benzoyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | (3.44) | 417.3 |

Example 381.3-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-1-methyl-1-(2-methyl-quinolin-4-yl)-urea

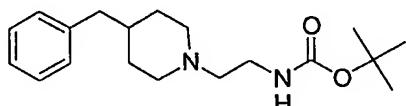
381A. (2-Bromo-ethyl)-carbamic acid tert-butyl ester.



To 1 N aqueous NaOH (200 mL) is added MeOH (400 mL) and the resulting solution is cooled to 20 °C. 2-Bromoethylamine hydrobromide (25.0 g, 122 mmol) is added in a single portion, followed by di-tert-butyl dicarbonate (26.6 g, 122 mmol). The reaction mixture is stirred for 2.5 h. The MeOH is removed on a rotary evaporator, and the aqueous suspension is extracted with CH₂Cl₂ (2 x 175 mL). The combined organic extracts are extracted with 5% aqueous citric acid (300 mL), dried (MgSO₄), filtered, and evaporated to provide the title compound.

381B. [2-(4-Benzyl-piperidin-1-yl)-ethyl]-carbamic acid tert-butyl ester

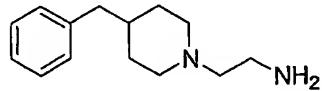
10



A mixture of 4-benzyl-piperidine (876 mg, 5.0 mmol), (2-bromo-ethyl)-carbamic acid tert-butyl ester (1.12 g, 5.0 mmol) and DIPEA (650 mg, 5 mmol) in THF (30 mL) is heated at reflux for 15 h. The solution is poured into ether (150 mL) and extracted with saturated Na₂CO₃ (2 x 50 mL) and brine (30 mL), dried (Na₂SO₄),

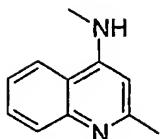
15 filtered and concentrated to provide a crude oil. Flash chromatography (EtOAc/heptane: 3/2) provides the title compound.

381C. 2-(4-Benzyl-piperidin-1-yl)-ethylamine



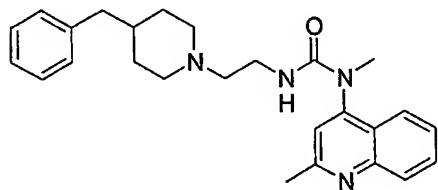
[2-(4-Benzyl-piperidin-1-yl)-ethyl]-carbamic acid tert-butyl ester (1.34 g, 4.2 mmol) is dissolved in CHCl₃ (3 mL) and treated with TFA (3 mL) for 2 h at 20°C. The solvent is evaporated, the residue dissolved CH₂Cl₂ (100 mL) and washed with 1M aqueous NaOH (2 x 30 mL). The organic layer is dried (Na₂SO₄), filtered and concentrated to provide the title compound.

381D. Methyl-(2-methyl-quinolin-4-yl)-amine



A mixture of 4-chloro-2-methyl-quinoline (4.36 g, 24.5 mmol) and benzylmethylamine (3.13 g, 25.8 mmol) is heated under N₂ at 120°C for 12 h. The residue is dissolved in CH₂Cl₂ (50 ml) and washed successively with aqueous saturated Na₂CO₃ (50 mL) and 1M aqueous NaOH (50 ml). The CH₂Cl₂ layer is evaporated, and the residue is dissolved in MeOH (400 mL) and 4M HCl in dioxane (12 mL). 10% Pd-C (410 mg) are added and the suspension is hydrogenated for 15 h under ambient pressure. The reaction mixture is filtered through a pad of Celite. 1M aqueous NaOH (100 mL) is added and the filtrate is evaporated. The residue is dissolved in water and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts are dried and evaporated to provide the title compound.

381E. 3-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-1-methyl-1-(2-methyl-quinolin-4-yl)-urea



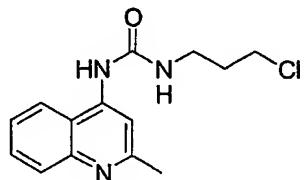
To a stirred solution of CDI (178 mg, 1.1 mmol) in DMSO (5 mL) is added a solution of 2-(4-benzyl-piperidin-1-yl)-ethylamine (218 mg, 1 mmol) in DMSO (1 mL). The reaction mixture is stirred at 20 °C for 3 h. Methyl-(2-methyl-quinolin-4-yl)-amine (173 mg, 1 mmol) is added. To the resulting solution is added in a single portion NaHMDS (2 M in THF, 1.25 mL, 2.5 mmol). The reaction mixture is stirred at 20 °C for 24 h, then H₂O (0.4 mL) is added. The reaction mixture is evaporated and the residue purified by preparative HPLC to provide the title compound.

| | Example | t _r | MS (ES+) |
|------|--|----------------|-------------|
| 381. | 3-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-1-methyl-1-(2-methyl-quinolin-4-yl)-urea | 0.58 | 417.12 |

| | | | |
|--|----------------------------|--|--|
| | methyl-quinolin-4-yl)-urea | | |
|--|----------------------------|--|--|

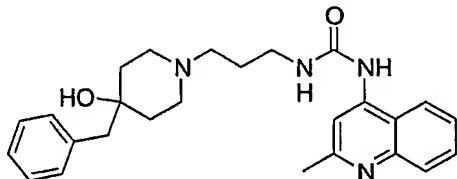
Example 382:**1-[3-(4-Benzyl-4-hydroxy-piperidin-1-yl)-propyl]-3-(2-methyl-quinolin-4-yl)-urea**

- 5 **382A.** 1-(3-Chloro-propyl)-3-(2-methyl-quinolin-4-yl)-urea



The title compound is prepared from 4-amino-2-methylquinoline and 3-chloropropylisocyanate by the method used in the preparation of Example 1A, 1-(2-chloroethyl)-3-(2-methyl-quinol-4-yl)-urea.

- 10 **382B.** 1-[3-(4-Benzyl-4-hydroxy-piperidin-1-yl)-propyl]-3-(2-methyl-quinolin-4-yl)-urea



- 15 Prepared from 4-hydroxy-4-benzyl-piperidine and 1-(3-chloro-propyl)-3-(2-methyl-quinolin-4-yl)-urea using the method exemplified with Example 341, 1-[2-(4-hydroxy-4-p-tolyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea.

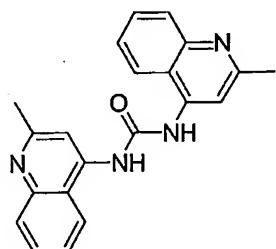
The following compounds are prepared in an analogous fashion.

| | Example | t _r | MS (ES+) |
|------|--|----------------|-------------|
| 382. | 1-[3-(4-Benzyl-4-hydroxy-piperidin-1-yl)-propyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.90 | 433.2 |

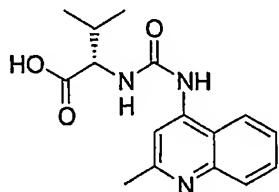
| | | | |
|------|---|------|-------|
| | methyl-quinolin-4-yl)-urea | | |
| 383. | 1-[3-(4-Benzyl-4-hydroxy-piperidin-1-yl)-propyl]-3-quinolin-4-yl-urea | 0.86 | 419.2 |

Example 384.**1-[*(S*)-1-(4-Benzyl-piperidin-1-ylmethyl)-2-methyl-propyl]-3-(2-methyl-quinolin-4-yl)-urea.**

5 384A. 1,3-Bis-(2-methyl-quinolin-4-yl)-urea



To a suspension of 4-amino-2-methylquinoline (20.24 g, 128 mmol) in THF (100 mL) is added CDI (13.9 g, 85 mmol). The mixture is heated at reflux for 15 h. The resulting precipitate is filtered, stirred with water (100 mL) for 6 h and filtered again. The filtercake is washed with water (20 mL), THF (20 mL) and dried to provide the title compound.

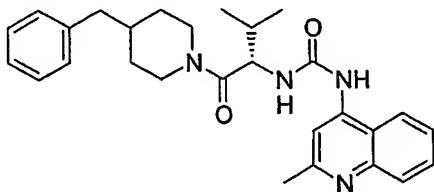
10 384B. (*S*)-3-Methyl-2-[3-(2-methyl-quinolin-4-yl)-ureido]-butyric acid

A suspension of 1,3-bis-(2-methyl-quinolin-4-yl)-urea (342.4 mg, 1 mmol), valin 15 methyl ester hydrochloride (167.6 mg, 1 mmol) and DIPEA (0.34 mL, 2 mmol) in MeOH (10mL) is heated at 80°C for 15 h. The solvent is evaporated and the

residue is dissolved in 6N aqueous HCl (6 mL). The reaction mixture is heated at 90°C for 12 h. Evaporation and purification by preparative HPLC provides the title compound.

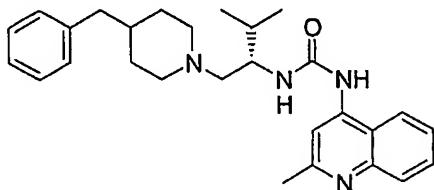
384C. 1-[(S)-1-(4-Benzyl-piperidine-1-carbonyl)-2-methyl-propyl]-3-(2-methyl-

5 **quinolin-4-yl)-urea**



To a solution of (S)-3-methyl-2-[3-(2-methyl-quinolin-4-yl)-ureido]-butyric acid hydrochloride (337.8 mg, 1 mmol), 4-benzylpiperidine (175.3 mg, 1 mmol), HOEt (183 mg, 1.2 mmol) and TEA (0.35 mL, 2.5 mmol) in DMF (10 mL) is added EDC (230.0 mg, 1.2 mmol). The mixture is stirred for 15h at room temperature and then quenched with sat. aqueous Na₂CO₃ (30 mL). The aqueous phase is extracted with CH₂Cl₂ (3x20 mL). The combined extracts are dried (Na₂SO₄), filtered and evaporated. The residue is purified by flash chromatography (SiO₂, CH₂Cl₂ / MeOH, 5/1) to provide the title compound.

15 **384D. 1-[(S)-1-(4-Benzyl-piperidin-1-ylmethyl)-2-methyl-propyl]-3-(2-methyl-**
 quinolin-4-yl)-urea.



To a solution of 1-[(S)-1-(4-benzyl-piperidine-1-carbonyl)-2-methyl-propyl]-3-(2-methyl-quinolin-4-yl)-urea in THF (10 mL) is added at 0°C LiAlH₄ (40mg, 1 mmol).
20 The reaction mixture is stirred at room temperature for 15 h and then quenched with EtOAc (1 mL) and sat. NaHCO₃ (0.2 mL). The resulting precipitate is removed by filtration and the filtercake washed with MeOH (2x5 mL). The mixture is

evaporated and the residue purified by TLC (SiO_2 , $\text{CH}_2\text{Cl}_2 / \text{MeOH}$, 5/1) to provide the title compound.

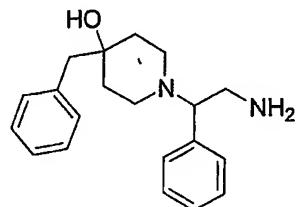
The following compounds are prepared in an analogous fashion.

| | Example | t_r | MS (ES+) |
|------|---|-------|-------------|
| 384. | 1-[(S)-1-(4-Benzyl-piperidin-1-ylmethyl)-2-methyl-propyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.78 | 445.25 |
| 385. | 1-[(S)-1-Benzyl-2-(4-benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.82 | 493.24 |
| 386. | 1-[(S)-1-(4-Benzyl-piperidin-1-ylmethyl)-3-methyl-butyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.81 | 459.27 |
| 387. | 1-[(S)-2-(4-Benzyl-piperidin-1-yl)-1-methyl-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.75 | 417.19 |

5 Example 388.

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-2-phenyl-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

388A. 1-(2-Amino-1-phenyl-ethyl)-4-benzyl-piperidin-4-ol

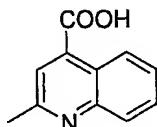


- 10 To a suspension of 4-benzyl-piperidin-4-ol (1.0 g, 5.2 mmol), benzaldehyde (0.83 g, 7.8 mmol) and MgSO_4 (0.31 g, 2.6 mmol) in 1-methyl-2-pyrrolidone (5 mL) is added acetone cyanohydrine (0.45 g, 5.2 mmol). The reaction mixture is heated at 50°C for 2 h, then cooled to room temperature and quenched with ice (20 g) and

sat. NaHCO_3 (50 mL). The aqueous phase is extracted with Et_2O (3x100 mL), the combined organic extracts are washed with sat. NaCl (20 mL), dried (Na_2SO_4), filtered and evaporated. The residue is dissolved in THF (20 mL) and added to a suspension of LiAlH_4 (1.1 g, 27.6 mmol) in THF (80 mL) at 0°C. The reaction mixture is stirred for 15 h at room temperature and quenched with EtOAc (250 mL), MeOH (20 mL) and sat. NaHCO_3 (5 mL). The precipitate is filtered off, washed with MeOH (20 mL) and the filtrate evaporated. Purification by preparative HPLC provides the title compound.

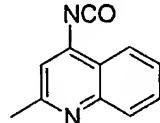
388B. 2-Methyl-quinoline-4-carboxylic acid

10



The compound is prepared from isatin and acetone using the method of Keneko C. et al., Chem. Pharm. Bull. (1980) 28, 1157-1171.

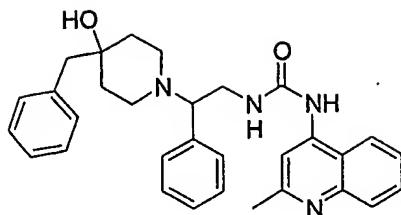
388C. 4-Isocyanato-2-methyl-quinoline



15 To a solution of 2-methyl-quinoline-4-carboxylic acid (276 mg, 1.2 mmol) in DMF (4 mL) at 0°C is added triethylamine (1.22 mg, 1.2 mmol) and slowly (30 min) DPPA (332 mg, 1.2 mmol). The reaction mixture is stirred for 2 h at 0°C and 12 h at 20 °C. The reaction is quenched with ice (10 g) and extracted with Et_2O (6 x 30 mL). The combined organic extracts are washed successively with saturated NaHCO_3 (2 x 15 mL) and water (2 x 10 mL), and are evaporated without heating in vacuo. The residue is dissolved in dry toluene and heated at reflux for 2h. The resulting solution is carried forward without further isolation of the title compound.

20

388D. 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-2-phenyl-ethyl]-3-(2-methyl-quinolin-4-yl)-urea



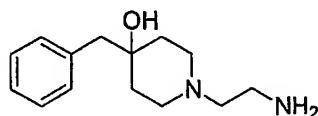
To a solution of 1-(2-amino-1-phenyl-ethyl)-4-benzyl-piperidin-4-ol (54.3 mg, 0.18 mmol) in CH₂Cl₂ is added a freshly prepared solution of 4-isocyanato-2-methyl-quinoline (33.8 mg, 0.16 mmol) in toluene (2 mL). The mixture is stirred for 15 h at 5 20 °C. Evaporation of the solvent and purification by HPLC provides the title compound.

| | Example | t _r | MS (ES+) |
|------|--|----------------|----------|
| 388. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-2-phenyl-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.67 | 495.41 |

Example 389.

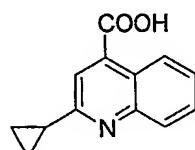
10 **1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-cyclopropyl-quinolin-4-yl)-urea**

389A. 1-(2-Amino-ethyl)-4-benzyl-piperidin-4-ol



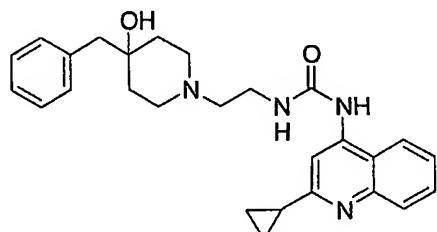
The title compound is prepared from 4-hydroxy-4-benzyl-piperidine using the method for the preparation of Example 381C.

15 **389B. 2-Cyclopropyl-quinoline-4-carboxylic acid**



The compound is prepared from isatin and cyclopropylmethylketone using the method of Keneko C. et al., Chem. Pharm. Bull. (1980) 28, 1157-1171.

389C. 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-cyclopropyl-quinolin-4-yl)-urea



5

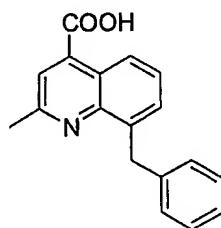
The compound is prepared from 1-(2-amino-ethyl)-4-benzyl-piperidin-4-ol and 2-cyclopropyl-quinoline-4-carboxylic acid according to the method described for Example 388D.

| | Example | t _r | MS (ES+) |
|-------------|--|----------------|-------------|
| 389. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-cyclopropyl-quinolin-4-yl)-urea | 1.16 | 445.2 |

10 **Example 390.**

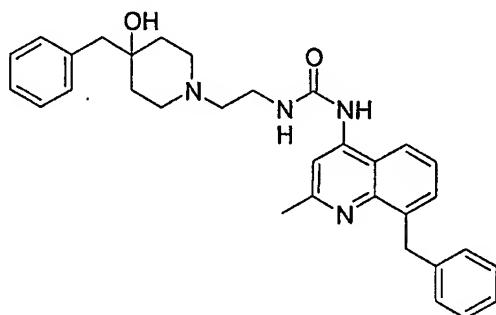
1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(8-benzyl-2-methyl-quinolin-4-yl)-urea

390A. 8-Benzyl-2-methyl-quinoline-4-carboxylic acid



The compound is prepared from 2-benzylaniline, acetaldehyde and pyruvic acid using the method of Irving, Clifton, J. Chem. Soc. (1959) 288.

390B. 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(8-benzyl-2-methyl-quinolin-4-yl)-urea



5

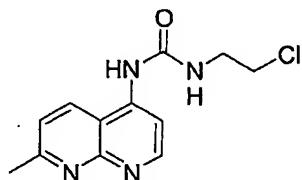
The compound is prepared from 1-(2-amino-ethyl)-4-benzyl-piperidin-4-ol and 8-benzyl-2-methyl-quinoline-4-carboxylic acid according to the method described for Example 388D.

| | Example | t _r | MS (ES+) |
|------|--|----------------|-------------|
| 390. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(8-benzyl-2-methyl-quinolin-4-yl)-urea | 0.78 | 509.13 |

10 **Example 391.**

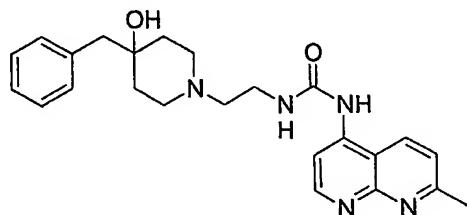
1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(7-methyl-[1,8]naphthyridin-4-yl)-urea

391A. 1-(2-Chloro-ethyl)-3-(2-methyl-[1,8]naphthyridin-4-yl)-urea



Prepared from 2-methyl-[1,8]naphthyrid-4-yl amine (Barlin GB, Tan WL, "Potential Antimalarials. I 1,8-naphthyridines", Aust J Chem (1984) 37, 1065-1073. Radivov R, Haimova M, Simova E "Synthesis of 4-Amino-3-Pyridyl and 4-Amino-5-Pyrimidyl Aryl Ketones and Related Compounds via an ortho-Lithiation Reaction", 5 Synthesis (1986), 886-891), using the method for the preparation of 1-(2-chloroethyl)-3-quinolin-4-yl-urea.

391B. 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(7-methyl-[1,8]naphthyridin-4-yl)-urea



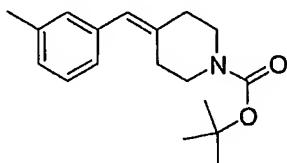
10 Prepared from 4-benzyl-4-hydroxypiperidine and 1-(2-chloro-ethyl)-3-(2-methyl-[1,8]naphthyridin-4-yl)-urea according to the method used in the preparation of Example 368C.

| | Example | t _r | MS (ES+) |
|------|--|----------------|-------------|
| 391. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(7-methyl-[1,8]naphthyridin-4-yl)-urea | 0.79 | 420.2 |

Example 392.

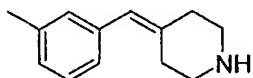
15 **1-{2-[4-(3-Methyl-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea**

392A. 4-(3-Methyl-benzylidene)-piperidine-1-carboxylic acid tert-butyl ester



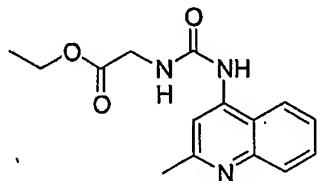
Sodium hydride (0.4 g, 16.6 mmol) is added to dry DMSO (30 mL) and the mixture is heated at 80°C for 1 h. After cooling to 20°C 4-fluorophenylmethyl triphenylphosphonium chloride (4.46 g, 11 mmol) is added portionwise under nitrogen, and the mixture is stirred for 15 min. Then 4-piperidone-1-carboxylic acid
 5 tert-butyl ester (2 g, 10 mmol) is added and the mixture is stirred for 15 h at room temperature followed by heating to 80°C for 8 h. The reaction mixture is cooled to room temperature and poured onto ice (75 g). The resulting mixture is extracted with ether (3 x 120 mL). The organic extracts are dried over sodium sulfate and evaporated. The resulting oil is purified by flash chromatography (SiO₂,
 10 EtOAc/heptane 1/5) to provide the title compound.

392B. 4-(3-Methyl-benzylidene)-piperidine

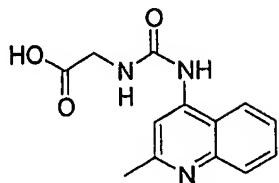


To a solution of 4-(3-methyl-benzylidene)-piperidine-1-carboxylic acid tert-butyl ester (287.4 mg, 1 mmol) in CH₂Cl₂ (1 mL) TFA (1 mL) is added. The solution is
 15 stirred for 2 h at 20°C. The solvent is evaporated, the residue dissolved CH₂Cl₂ (75 mL) and washed with 1M aqueous NaOH (2 x 20 mL). The organic layer is dried (Na₂SO₄), filtered and concentrated to provide the title compound.

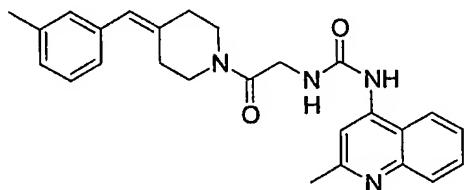
392C. [3-(2-Methyl-quinolin-4-yl)-ureido]-acetic acid ethyl ester



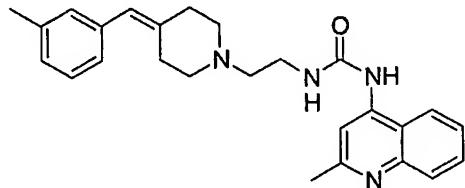
20 A suspension of 4-amino-2-methylquinoline (4.0 g, 25.3 mmol) in dry THF (80 mL) is cooled to -14 °C and ethyl isocyanatoacetate (3.3 mL, 27.4 mmol) is added dropwise under vigorous stirring. The reaction is warmed to room temperature and stirred for 4 h. Further ethyl isocyanatoacetate (0.6 mL, 5 mmol) is added and the reaction mixture stirred for 15 h. The solvent is evaporated and the residue
 25 crystallized from CHCl₃-heptane (1/5) to provide the title compound.

392D. (3-Quinolin-4-yl-ureido)-acetic acid

[3-(2-Methyl-quinolin-4-yl)-ureido]-acetic acid ethyl ester (7.2 g, 25 mmol) is suspended in 6N aqueous HCl (250 mL), and the mixture is heated at 80°C for 15 h. The mixture is cooled, filtered from the resulting precipitate and the solid dried to provide the title compound as hydrochloride salt.

392E. 1-{2-[4-(3-Methyl-benzylidene)-piperidin-1-yl]-2-oxo-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

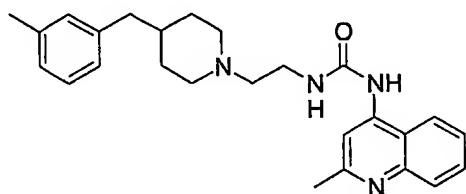
A suspension of (3-quinolin-4-yl-ureido)-acetic acid hydrochloride (281.7 mg, 1 mmol), 4-(3-methyl-benzylidene)-piperidine (187.3 mg, 1 mmol), TEA (1 mL, 7 mmol) in DMF (4 mL) and T₃P (50% in EtOAc, 1 mL, 1.7 mmol) is stirred for 2 h at room temperature. The DMF is evaporated, the residue dissolved in CH₂Cl₂ (150 mL) and washed with 1M aqueous NaOH (50 mL) and brine (30 mL). The organic phase is dried (Na₂SO₄), filtered and evaporated to provide the crude title compound.

392F. 1-{2-[4-(3-Methyl-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

To a suspension of LiAlH₄ (100 mg, 2.6 mmol) in THF (40 mL) is added a solution of crude 1-[2-[4-(3-methyl-benzylidene)-piperidin-1-yl]-2-oxo-ethyl]-3-(2-methyl-quinolin-4-yl)-urea (1 mmol) in THF (10 mL) and the mixture is stirred at room temperature for 15 h. The suspension is poured slowly into EtOAc (200 mL) and 5 MeOH (10 mL) and, subsequently, sat. NaHCO₃ (dropwise, total of 1.5 mL) is added. The precipitate is filtered off and washed with MeOH (2x20 mL). The filtrate is dried (Na₂SO₄), filtered and evaporated. The residue is purified by flash chromatography (SiO₂, CH₂Cl₂-MeOH, 10:1) to provide the title compound.

The following compounds are prepared in an analogous fashion.

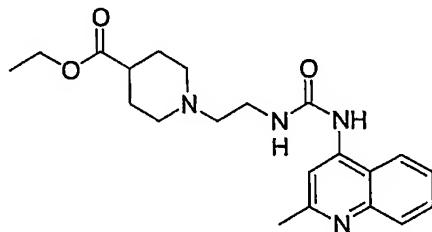
| | Example | t _r | MS (ES+) |
|------|--|----------------|-------------|
| 392. | 1-[2-[4-(3-Methyl-benzylidene)-piperidin-1-yl]-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.77 | 415.18 |
| 393. | 1-[2-[4-(4-Methyl-benzylidene)-piperidin-1-yl]-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.77 | 415.19 |
| 394. | 1-[2-[4-(2-Methyl-benzylidene)-piperidin-1-yl]-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.76 | 415.21 |
| 395. | 1-[2-[4-(4-Methoxy-benzylidene)-piperidin-1-yl]-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.74 | 431.25 |
| 396. | 1-[2-[4-(4-Fluoro-benzylidene)-piperidin-1-yl]-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 0.75 | 419.21 |
| 397. | 1-[2-[4-(4-Bromo-benzylidene)-piperidin-1-yl]-ethyl]-3-(2-methyl-quinolin-4-yl)-urea | 1.02 | 479.33 |

Example 398.**1-{2-[4-(3-Methyl-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea**

A suspension of 1-{2-[4-(3-methyl-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-
5 quinolin-4-yl)-urea (21 mg, 0.05 mmol), 2M aqueous HCl (0.5 mL, 1 mmol) and
Pd-C (10%, 5 mg) in MeOH (2 mL) is stirred under hydrogen atmosphere for 6 h.
The catalyst is filtered off and the filtrate evaporated to provide the title compound
as hydrochloride salt.

The following compounds are prepared in an analogous fashion.

| | Example | t _r | MS (ES+) |
|-------------|---|----------------|----------|
| 398. | 1-{2-[4-(3-Methyl-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.77 | 417.26 |
| 399. | 1-{2-[4-(2-Methyl-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.77 | 417.26 |
| 400. | 1-{2-[4-(4-Methoxy-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.74 | 433.25 |
| 401. | 1-{2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.75 | 421.23 |
| 402. | 1-{2-[4-(4-Methyl-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.76 | 417.27 |

Example 403.**1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-piperidine-4-carboxylic acid ethyl ester.**

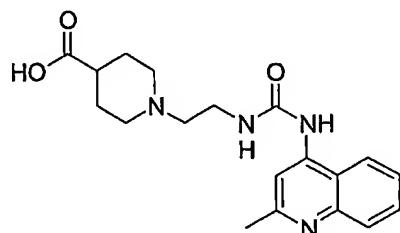
- 5 The compound is prepared from 1-(2-chloro-ethyl)-3-(2-methyl-quinolin-4-yl)-urea (Example 1A, 1.32 g, 5 mmol)) and ethyl nipecotate (1.57 g, 10 mmol) using the method of Example 1.

| | Example | t _r | MS (ES+) |
|------|--|----------------|-------------|
| 403. | 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-piperidine-4-carboxylic acid ethyl ester | 0.69 | 385.21 |

Example 404.

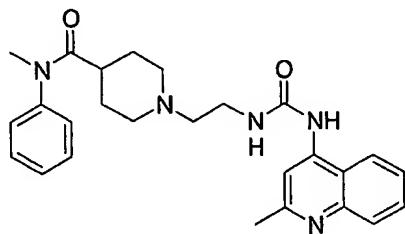
- 10 **1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-piperidine-4-carboxylic acid methyl-phenyl-amide**

404A. 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-piperidine-4-carboxylic acid dihydrochloride



1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid ethyl ester (0.9 g, 2.3 mmol) is dissolved in 6N aqueous HCl (10 mL) and the mixture is heated at 50°C for 48 h. The reaction mixture is evaporated and the residue is dried to provide the title compound as hydrochloride salt.

- 5 **404B.** 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid methyl-phenyl-amide



To a suspension of 1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid dihydrochloride (64.25 mg, 0.15 mmol), TEA (0.07 mL, 0.5 mmol) and N-methylaniline (11 mg, 0.1 mmol) in DMF (0.6 mL) is added T₃P (50% in EtOAc, 0.07 mL, 0.12 mmol) at room temperature. The mixture is stirred for 15 h, quenched with sat. Na₂CO₃ (5 mL) and extracted with CH₂Cl₂ (3x10 mL). The organic phases are dried (Na₂SO₄), filtered, evaporated and the residue purified by preparative HPLC to provide the title compound.

- 15 The following compounds are prepared in an analogous fashion.

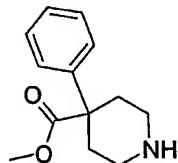
| | Example | t _r | MS (ES+) |
|-------------|---|----------------|----------|
| 404. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid methyl-phenyl-amide | 0.55 | 446.09 |
| 405. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid naphthalen-2-ylamide | 0.62 | 482.10 |
| 406. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid naphthalen-1-ylamide | 0.60 | 482.08 |
| 407. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}- | 0.54 | 446.11 |

| | | | |
|------|---|------|--------|
| | piperidine-4-carboxylic acid benzylamide | | |
| 408. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid phenethyl-amide | 0.56 | 460.12 |
| 409. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-methyl-amide | 0.56 | 460.09 |
| 410. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid methyl-phenethyl-amide | 0.58 | 474.12 |
| 411. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid (4-phenyl-butyl)-amide | 0.63 | 488.12 |
| 412. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-phenyl-amide | 0.66 | 522.11 |
| 413. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid (4-chloro-phenyl)-methyl-amide | 0.60 | 480.05 |
| 414. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid (4-bromo-phenyl)-amide | 0.62 | 509.98 |
| 415. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid (3-chloro-phenyl)-amide | 0.60 | 466.03 |
| 416. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid (2-chloro-phenyl)-methyl-amide | 0.58 | 480.05 |
| 417. | 1-{2-[4-(4-Benzyl-piperidine-1-carbonyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea | 0.66 | 514.12 |
| 418. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-phenethyl-amide | 0.69 | 550.13 |

| | | | |
|------|--|------|--------|
| 419. | 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-piperidine-4-carboxylic acid 4-bromo-benzylamide | 0.60 | 523.95 |
| 420. | 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-piperidine-4-carboxylic acid (3-phenyl-propyl)-amide | 0.60 | 474.12 |
| 421. | 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-piperidine-4-carboxylic acid benzyl-ethyl-amide | 0.65 | 474.49 |
| 422. | 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-piperidine-4-carboxylic acid methyl ester | 0.54 | 371.35 |

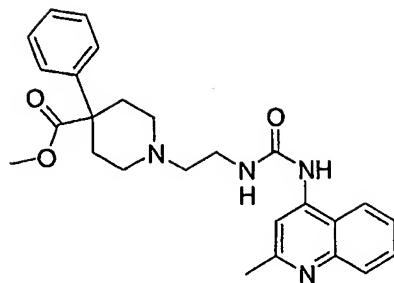
Example 423.**1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-4-phenyl-piperidine-4-carboxylic acid methyl ester.**

5 **423A.** 4-Phenyl-piperidine-4-carboxylic acid methyl ester.



To a solution of 4-phenyl-piperidine-4-carboxylic acid tosylate (4.6 g, 20 mmol) in MeOH (25 mL) is added TMSCl (10 mL) and the reaction mixture is stirred at 50°C for 15 h. The reaction mixture is cooled and evaporated. The residue is taken up in 10 MeOH (5 mL), poured into sat. Na₂CO₃ (100 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts are dried (Na₂SO₄), filtered and evaporated to provide the title compound.

423B. 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-4-phenyl-piperidine-4-carboxylic acid methyl ester



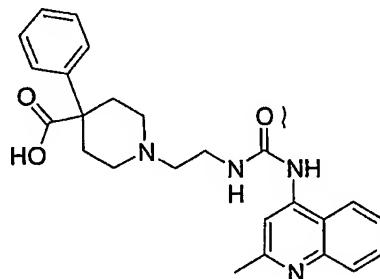
The compound is prepared from 1-(2-chloro-ethyl)-3-(2-methyl-quinolin-4-yl)-urea (Example 1A, 2.6 g, 10 mmol)) and 4-phenyl-piperidine-4-carboxylic acid methyl ester (4.38 g, 20 mmol) using the method of Example 1.

| | Example | t _r | MS (ES+) |
|------|--|----------------|-------------|
| 423. | 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-4-phenyl-piperidine-4-carboxylic acid methyl ester | 0.59 | 447.07 |

5

Example 424.

1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-4-phenyl-piperidine-4-carboxylic acid.



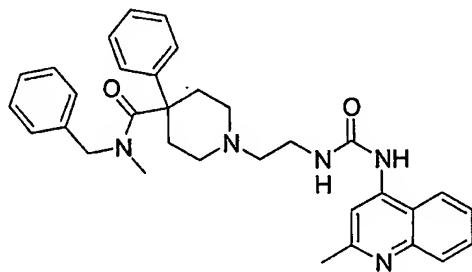
- 10 A solution of 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-4-phenyl-piperidine-4-carboxylic acid methyl ester (1.25 g, 2.8 mmol) in 6N aqueous HCl (10 mL) is heated at 90°C for 48 h. The reaction mixture is evaporated to provide the title compound as dihydrochloride salt.

| | Example | t _r | MS (ES+) |
|--|---------|----------------|-------------|
| | | | |

| | | | |
|------|---|------|--------|
| 424. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid | 0.60 | 433.38 |
|------|---|------|--------|

Example 425.

1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amid.



5

The compound is prepared from 1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid dihydrochloride and benzylmethylamine using the method of Example 404B.

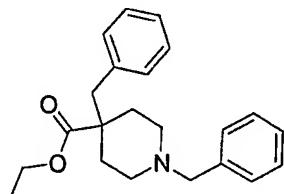
The following compounds are prepared in an analogous fashion.

| | Example | t _r | MS (ES+) |
|------|--|----------------|-------------|
| 425. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide | 0.69 | 536.10 |
| 426. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid naphthalen-2-ylamide | 0.78 | 558.11 |
| 427. | 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid methyl-phenethyl-amide | 0.70 | 550.15 |

| | | | |
|------|---|------|--------|
| 428. | 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-4-phenyl-piperidine-4-carboxylic acid benzyl-ethylamide | 0.74 | 550.52 |
| 429. | 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-4-phenyl-piperidine-4-carboxylic acid dimethylamide | 0.63 | 460.40 |
| 430. | 1-[2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl]-4-phenyl-piperidine-4-carboxylic acid diethylamide | 0.68 | 488.49 |

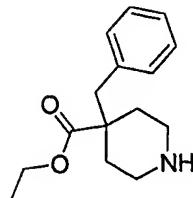
Example 431.**4-Benzyl-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid**

- 5 431A. 1,4-Dibenzyl-piperidine-4-carboxylic acid ethyl ester



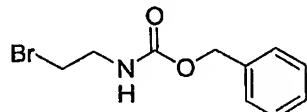
To a solution of NaHMDS in THF (1M, 80 mL, 80 mmol) at -78°C is added a solution of ethyl nipecotate (5.5 g, 35 mmol) in THF (20 mL). The mixture is stirred at -78°C for 30 min and then warmed to room temperature. A solution of 10 benzylbromide (9.5 mL, 80 mmol) in THF (40 mL) is added (15 min) to the solution and stirring is continued for 15 h. The mixture is poured into ether (200 mL) and extracted with 1M aqueous HCl (3x50 mL). The aqueous extracts are washed with ether (50 mL) and adjusted to pH 14 with solid Na₂CO₃ and 33% NaOH and then extracted with CH₂Cl₂ (3x 100 mL). The organic extracts are dried (Na₂SO₄), 15 filtered and evaporated, the residue purified by flash chromatography (CH₂Cl₂-MeOH 10:1) to provide the title compound.

- 431B. 4-Benzyl-piperidine-4-carboxylic acid ethyl ester



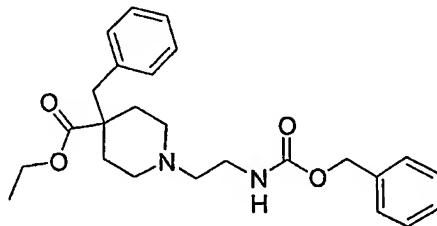
1,4-Dibenzyl-piperidine-4-carboxylic acid ethyl ester (11.8 g, 35 mmol) is dissolved in MeOH (200 mL) and 1M aqueous HCl (40 mL) and Pd-C (10%, 1 g) are added. The mixture is hydrogenated (7 bar, 70°C) for 15h. The catalyst is filtered off and the solvent evaporated to provide the title compound.

431C. (2-Bromo-ethyl)-carbamic acid benzyl ester



2-Bromoethylamine hydrobromide (15 g, 73 mmol) and N-(benzyloxycarbonyloxy)succinimide (15.5 g, 62 mmol) are suspended in CH₂Cl₂ (150 mL) at 0°C. TEA (9 mL, 65 mmol) is added slowly keeping the temperature at 0°C. After 1h the mixture is washed with 0.5M aqueous KHSO₄ (50 mL) and brine (50 mL), the organic phase is dried (Na₂SO₄), filtered and evaporated to provide the title compound.

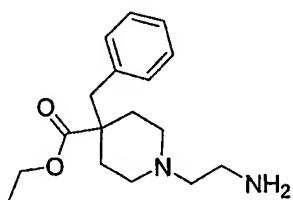
431D. 4-Benzyl-1-(2-benzyloxycarbonylamino-ethyl)-piperidine-4-carboxylic acid ethyl ester



4-Benzyl-piperidine-4-carboxylic acid ethyl ester (2.5 g, 10 mmol), (2-bromo-ethyl)-carbamic acid benzyl ester (2.58 g, 10 mmol) and DIPEA (1.7 mL, 10 mmol) are dissolved in THF (50 mL) and heated at 80°C for 15 h. The mixture is poured into Et₂O (200 mL) and washed with sat. Na₂CO₃ (50 mL). The ether phase is

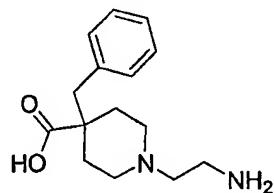
extracted with 1M aqueous HCl (3x50 mL), the aqueous extracts washed with ether (50 mL) and adjusted to pH 14 with cooled 33% aqueous NaOH. The aqueous phase is extracted with CH₂Cl₂ (4x50 mL). The organic extracts are dried (Na₂SO₄), filtered and evaporated to provide the title compound.

5 **431E. 1-(2-Amino-ethyl)-4-benzyl-piperidine-4-carboxylic acid ethyl ester**



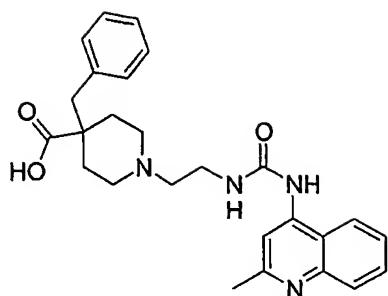
4-Benzyl-1-(2-benzyloxycarbonylaminooethyl)-piperidine-4-carboxylic acid ethyl ester (4.25 g, 10 mmol) is dissolved in MeOH (100 mL) and Pd-C (10%, 0.5 g) is added. The mixture is hydrogenated (7 bar, 20°C) for 2h. The catalyst is filtered off
10 and the solvent evaporated to provide the title compound.

431F. 1-(2-Amino-ethyl)-4-benzyl-piperidine-4-carboxylic acid



1-(2-Amino-ethyl)-4-benzyl-piperidine-4-carboxylic acid ethyl ester (2.5 g, 10 mmol) is dissolved in 6N aqueous HCl (40 mL) and the mixture heated at 90°C for
15 96 h. The reaction mixture is evaporated to provide the title compound as hydrochloride salt.

431G. 4-Benzyl-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid

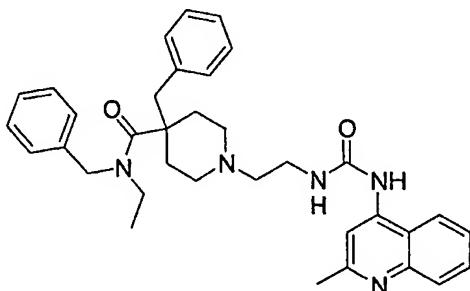


1-(2-Amino-ethyl)-4-benzyl-piperidine-4-carboxylic acid dihydrochloride (3.35 g, 10 mmol), 1,3-bis-(2-methyl-quinolin-4-yl)-urea (3.43 g, 10 mmol) and TEA (5 mL, 36 mmol) are suspended in THF (50 mL) and heated at reflux for 48 h. The solvent is
5 evaporated and the residue purified by HPLC to provide the title compound.

| | Example | t _r | MS (ES+) |
|------|---|----------------|----------|
| 431. | 4-Benzyl-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid | 0.62 | 477.39 |

Example 432.

4-Benzyl-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-ethyl-amide



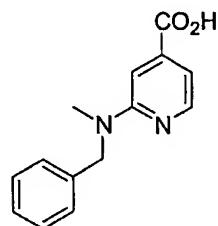
10

The compound is prepared from 4-benzyl-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid and benzylethylamine using the method of Example 257C.

| | Example | t _r | MS (ES+) |
|------|--|----------------|-------------|
| 432. | 4-Benzyl-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-ethyl-amide | 0.75 | 564.45 |
| 433. | 4-Benzyl-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid methyl ester | 0.67 | 461.46 |

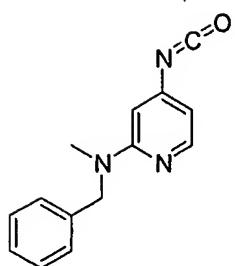
Example 434.**1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-(benzyl-methyl-amino)-pyridin-4-yl]-urea**

5 434A. 2-(Benzyl-methyl-amino)-isonicotinic acid



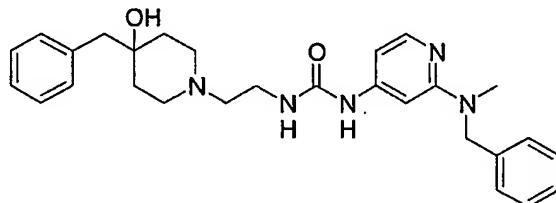
A mixture of 2-chloro-pyridine-4-carboxylic acid (300 mg, 1.9 mmol), benzylmethylamine (230 mg, 1.9 mmol) and triethylamine (192 mg, 1.9 mmol) is heated at 120°C for 12 h. The residue is dissolved in CH₂Cl₂ (30 mL) and extracted with 1M aqueous NaOH (3 x 5 mL). The aqueous layer is adjusted to pH 1-2 with 12N aqueous HCl and extracted with EtOAc (6 x 5 mL). The organic extracts are combined, dried (MgSO₄), and evaporated to provide the title compound.

10 434B. 2-(Benzyl-methyl-amino)-4-isocyanato-pyridine



The compound is prepared from 2-(benzyl-methyl-amino)-pyridine-4-carboxylic acid (780 mg, 3.2 mmol) using the method described for Example 388C.

434C. 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-(benzyl-methyl-amino)-5-pyridin-4-yl]-urea

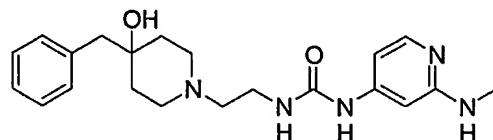


The compound is prepared from 1-(2-amino-ethyl)-4-benzyl-piperidin-4-ol (93 mg, 0.40 mmol) and 2-(benzyl-methyl-amino)-4-isocyanato-pyridine (95.7 mg, 0.40 mmol) using the method described for Example 388D.

10 The following compounds are prepared in an analogous fashion.

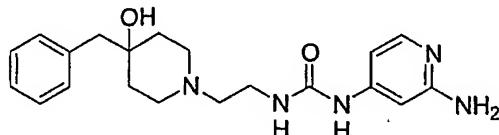
| | Example | t _r | MS (ES+) |
|-------------|--|----------------|----------|
| 434. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-(benzyl-methyl-amino)-pyridin-4-yl]-urea | 0.74 | 474.2 |
| 435. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-(benzyl-methyl-amino)-6-methyl-pyridin-4-yl]-urea | 0.69 | 488.4 |
| 436. | 1-[2-(Benzyl-methyl-amino)-6-methyl-pyridin-4-yl]-3-[2-(4-benzyl-piperidin-1-yl)-ethyl]-urea | 0.75 | 472.27 |
| 437. | 1-[2-(Benzyl-methyl-amino)-pyridin-4-yl]-3-[2-(4-benzyl-piperidin-1-yl)-ethyl]-urea | 0.73 | 458.24 |

| | | | |
|------|--|------|--------|
| | benzyl-piperidin-1-yl)-ethyl]-urea | | |
| 438. | 1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-[2-(methyl-phenyl-amino)-pyridin-4-yl]-urea | 0.78 | 444.26 |
| 439. | 1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-pyrrolidin-1-yl-pyridin-4-yl)-urea | 0.76 | 408.10 |
| 440. | 1-[2-(Benzyl-phenethyl-amino)-pyridin-4-yl]-3-[2-(4-benzyl-piperidin-1-yl)-ethyl]-urea | 0.76 | 548.16 |
| 441. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-dimethylamino-pyridin-4-yl)-urea | 0.68 | 398.26 |
| 442. | 1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-dimethylamino-pyridin-4-yl)-urea | 0.72 | 382.29 |
| 443. | 1-[2-(Benzyl-ethyl-amino)-pyridin-4-yl]-3-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-urea | 0.67 | 488.46 |
| 444. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-(ethyl-methyl-amino)-pyridin-4-yl]-urea | 0.70 | 412.24 |
| 445. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-diallylamino-pyridin-4-yl)-urea | 0.68 | 488.40 |
| 446. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-dipropylamino-pyridin-4-yl)-urea | 0.69 | 480.45 |

Example 447.**1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methylamino-pyridin-4-yl)-urea**

- 5 A suspension of 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-(benzyl-methyl-amino)-pyridin-4-yl]-urea (Example 434., 0.3 g, 0.65 mmol), 2N aqueous HCl (0.65 mL, 1.3 mmol) and Pd-C 10 % (30 mg) in MeOH (20 mL) is stirred under hydrogen atmosphere for 96 h. The catalyst is filtered off and the reaction mixture evaporated to provide the title compound.
- 10 The following compounds are prepared in an analogous fashion.

| | Example | t _r | MS (ES+) |
|------|---|----------------|-------------|
| 447. | 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methylamino-pyridin-4-yl)-urea | 0.69 | 384.16 |
| 448. | 1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methylamino-pyridin-4-yl)-urea | 0.72 | 368.17 |

Example 449.**1-(2-Amino-pyridin-4-yl)-3-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-urea**

- 15 The compound is prepared from 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-diallylamino-pyridin-4-yl)-urea (Example 445.) using the method described in

Laguzza B.C., Ganem B., "A new protecting group for amines. Synthesis of Anticapsin from L-Tyrosine", Tetrahedron Lett. (1981) 22, 1483-1486.

| | Example | t_r | MS (ES+) |
|------|---|-------|-------------|
| 449. | 1-(2-Amino-pyridin-4-yl)-3-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-urea | 0.65 | 450.42 |

EXAMPLE 450. IN VITRO BIOLOGICAL CHARACTERIZATION

- 5 The inhibitory activity of the compounds of general formula 1 on the actions of urotensin II can be demonstrated using the test procedures described hereinafter:

1) INHIBITION OF HUMAN [125 I]-UROTENSIN II BINDING TO A RABDOMYOSARCOMA CELL LINE

Whole cell binding of human [125 I]-urotensin II is performed using human-derived
10 TE-671 rhabdomyosarcoma cells (Deutsche Sammlung von Mikroorganismen und Zellkulturen, cell line #ACC-263), by methods adapted from a whole cell endothelin binding assay (Breu V et al, In vitro characterization of Ro-46-2005, a novel synthetic non-peptide antagonist of ET_A and ET_B receptors. FEBS Lett. 1993, 334, 210-214).

- 15 The assay is performed in 250 μ L Dulbecco's Modified Eagle Medium, pH 7.4 (GIBCO BRL, CatNo 31885-023), including 25 mM HEPES (Fluka, CatNo 05473), 1.0 % DMSO (Fluka, CatNo 41644) and 0.5% (w/v) BSA Fraction V (Fluka, CatNo 05473) in polypropylene microtiter plates (Nunc, CatNo 442587). 300'000 suspended cells are incubated with gentle shaking for 4 h at 20°C with 20 pM
20 human [125 I]Urotensin II (Anawa Trading SA, Wangen, Switzerland, 2130Ci/mmol) and increasing concentrations of unlabeled antagonist. Minimum and maximum binding are derived from samples with and without 100 nM unlabelled U-II, respectively. After the 4 h incubation period, the cells are filtered onto GF/C filterplates (Packard, CatNo 6005174). The filter plates are dried, and then 50 μ L scintillation cocktail (Packard, MicroScint 20, CatNo 6013621) is added to each
25

well. The filterplates are counted in a microplate counter (Packard Bioscience, TopCount NXT).

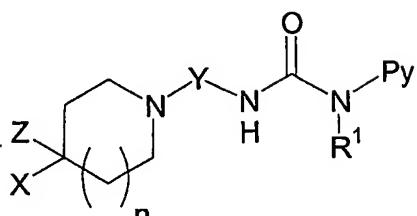
All test compounds are dissolved and diluted in 100% DMSO. A ten-fold dilution into assay buffer is performed prior to addition to the assay. The final 5 concentration of DMSO in the assay is 1.0%, which is found not to interfere with the binding. IC₅₀ values are defined as the concentration of antagonist inhibiting 50% of the specific binding of [¹²⁵I]human U-II. Specific binding is the difference between maximum binding and minimum binding, as described above. An IC₅₀ value of 0.206 nM is found for unlabeled human U-II. The compounds of the 10 invention are found to have IC₅₀ values ranging from 0.1 to 1000 nM in this assay.

2) INHIBITION OF HUMAN UROTENSIN II-INDUCED CONTRACTIONS ON ISOLATED RAT THORACIC AORTA :

Adult Wistar rats are anesthetized and exsanguinated. The proximal thoracic descending aorta is excised, dissected and a 3-5 mm ring is isolated. The 15 endothelium is removed by gentle rubbing of the intimal surface. The ring is suspended in a 10 mL isolated organ bath filled with Krebs-Henseleit solution (in mM; NaCl 115, KCl 4.7, MgSO₄ 1.2, KH₂PO₄ 1.5, NaHCO₃ 25, CaCl₂ 2.5, glucose 10) kept at 37° C and aerated with 95% O₂ and 5% CO₂. Indomethacin (10⁻⁵ M) is added to the Krebs-Henseleit solution to avoid eicosanoid generation. The ring is 20 stretched to a resting tension of 1 g. Changes of isometric force are measured using force transducers (EMKA Technologies SA, Paris, France). Following an equilibration period, the rings are briefly contracted with KCl (60 mM). Cumulative doses of human urotensin II (10⁻¹² M to 10⁻⁶ M) are added after a 10 min incubation with the test compound or its vehicle. Functional antagonism is measured as the 25 inhibition of maximal contraction to urotensin II.

CLAIMS

1. Compounds of the general formula 1.



5 wherein:

Py represents pyridin-4-yl mono-substituted in position 2 with -NR²R³; pyridin-4-yl disubstituted in position 2 with -NR²R³ and in position 6 with lower alkyl or arylalkyl; unsubstituted quinolin-4-yl; quinolin-4-yl mono-substituted in position 2 with lower alkyl; quinolin-4-yl di-substituted in position 2 with lower alkyl and in position 6, 7, or 8 with halogen, lower alkyl, or arylalkyl; 2-hydroxymethyl-quinolin-4-yl; 7-methyl-[1,8]naphthyridin-4-yl; 5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl; 8-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl; 2,3-dihydro-1H-pyrido[2,3-b]pyridin-4-yl; 1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl; 1-benzyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl;

10 X represents aryl; aryl-O-; arylalkyl-; lower alkyl-SO₂NR²-; aryl-SO₂NR²-; arylalkyl-SO₂NR²-; lower alkyl-CONR²-; aryl-CONR²-; arylalkyl-CONR²-; lower alkyl-NR³CONR²-; aryl-NR³CONR²-; arylalkyl-NR³CONR²-; aryl-CO-; arylalkyl-CO-; lower alkyl-NR²CO-; aryl-NR²CO-; arylalkyl-NR²CO-; or X and Z represent together with the carbon atom to which they are attached an exocyclic double bond which bears an aryl substituent.

15 Y represents -C(R⁴)(R⁵)(CH₂)_m- or -(CH₂)_mC(R⁴)(R⁵)-

Z represents hydrogen; in case X represents aryl or arylalkyl, Z represents hydrogen, hydroxyl, carboxyl, aryl-CONR²-; lower alkyl-NR²CO-, aryl-NR²CO- or arylalkyl-NR²CO-;

20 n represents the numbers 0 or 1;

m represents the numbers 1 or 2;

R¹ represents hydrogen or lower alkyl;

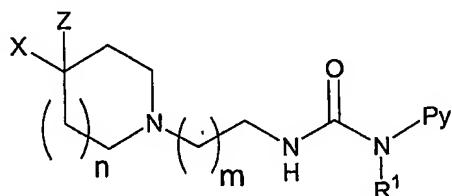
R² and R³ represent independently hydrogen, lower alkyl, or arylalkyl; in case R² and R³ are attached to the same nitrogen atom, R² and R³ together form with the nitrogen to which they are attached, a piperidine, pyrrolidine or morpholine ring;

R⁴ represents hydrogen, lower alkyl, aryl, arylalkyl, or forms together with R⁵ a 3-, 4-, 5-, or 6-membered saturated carbocyclic ring including the carbon atom to which R⁴ and R⁵ are attached as ring atoms;

R⁵ represents hydrogen, methyl, or forms together with R⁴ a 3-, 4-, 5-, or 6-membered saturated carbocyclic ring including the carbon atom to which R⁴ and R⁵ are attached as ring atoms;

and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates; as well as their pharmaceutically acceptable salts, solvent complexes, and morphological forms.

2. Compounds of the general formula 2,



General Formula 2

wherein:

Py represents 2-(benzyl-methyl-amino)-pyridin-4-yl; 2-(benzyl-methyl-amino)-6-methyl-pyridin-4-yl; 2-(benzylamino)-pyridin-4-yl; 2-benzylamino-6-methyl-pyridin-4-yl; 2-(dimethylamino)-pyridin-4-yl; 2-(dimethylamino)-6-methyl-pyridin-4-yl; 2-(methylamino)-pyridin-4-yl; 2-(methylamino)-6-methyl-pyridin-4-yl; 2-aminopyridin-4-yl; 2-amino-6-methyl-pyridin-4-yl; 2-(pyrrolidin-1-yl)-

pyridin-4-yl; quinol-4-yl; 2-methylquinol-4-yl; 2-cyclopropylquinol-4-yl; 8-benzyl-2-methyl-quinol-4-yl; [1,8]naphthyridin-4-yl; 7-methyl-[1,8]naphthyridin-4-yl; 5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl; 8-benzyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl; 8-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-4-yl; 2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl; 1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl; 1-benzyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl;

5 X represents aryl; aryl-O-; arylalkyl-; lower alkyl-SO₂NR²-; aryl-SO₂NR²-; arylalkyl-SO₂NR²-; lower alkyl-CONR²-; aryl-CONR²-; arylalkyl-CONR²-; lower alkyl-NR³CONR²-; aryl-NR³CONR²-; arylalkyl-NR³CONR²-; aryl-CO-; arylalkyl-CO-; lower alkyl-NR²CO-; aryl-NR²CO-; arylalkyl-NR²CO-;

10 10 Z represents hydrogen; in case X represents aryl or arylalkyl, Z represents hydrogen or hydroxyl;

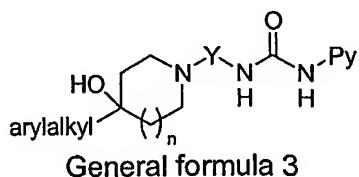
n represents the numbers 0 or 1;

m represents the numbers 1 or 2;

15 R¹ represents hydrogen or lower alkyl;

R² and R³ represent independently hydrogen, lower alkyl, or arylalkyl;

3. Compounds of general formula 3,



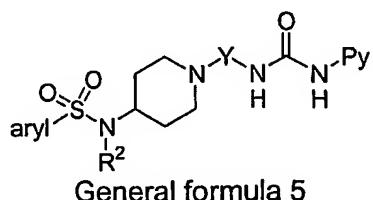
20 wherein n, Y and Py have the meaning given in general formula 1.

4. Compounds of general formula 4,



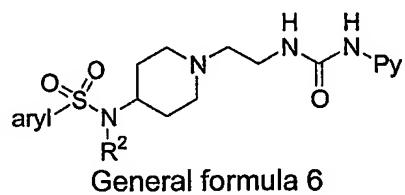
wherein n and Py has the meaning given in general formula 2.

5. Compounds of general formula 5,



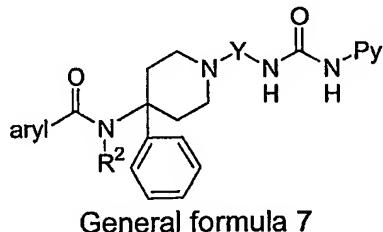
5 wherein R², Y and Py have the meaning given in general formula 1.

6. Compounds of general formula 6,



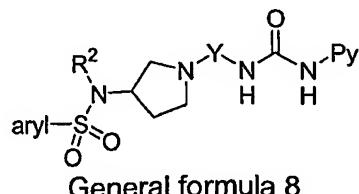
wherein R² and Py have the meaning given in general formula 2.

10 7. Compounds of general formula 7,



wherein R², Y and Py have the meaning given in general formula 1.

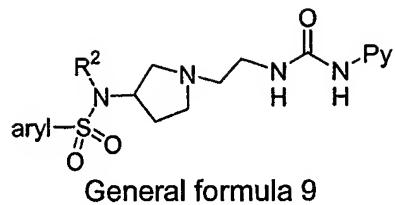
8. Compounds of general formula 8,



15

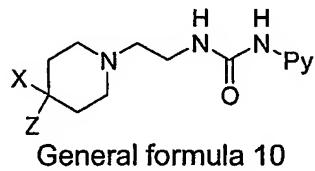
wherein R², Y and Py have the meaning given in general formula 1.

9. Compounds of general formula 9,



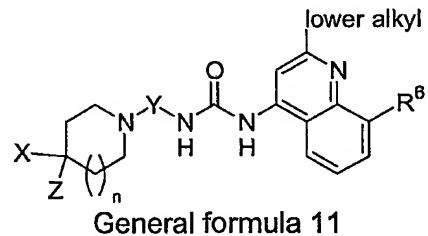
wherein R² and Py have the meaning given in general formula 2.

10. Compounds of general formula 10,



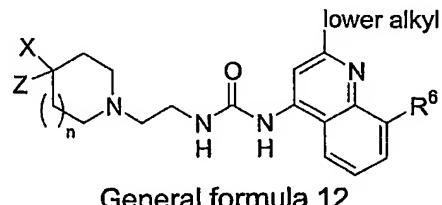
wherein X, Z and Py have the meaning given in general formula 1.

11. Compounds of general formula 11;



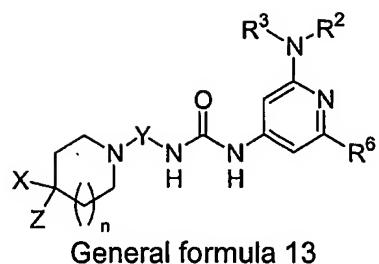
wherein R⁶ is hydrogen, lower alkyl, or arylalkyl; and n, X, Y, and Z have the meaning given in general formula 1.

12. Compounds of general formula 12,



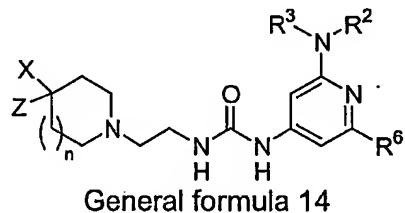
wherein R⁶ has the meaning given in general formula 11; and n, X and Z have the meaning given in general formula 2.

13. Compounds of general formula 13,



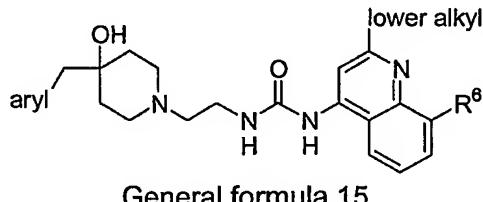
wherein R^6 has the meaning given in general formula 11; and n, R^2 , R^3 , X, Y, and Z have the meaning given in general formula 1.

5 14. Compounds of general formula 14,



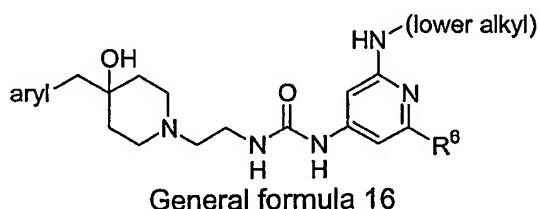
wherein R^6 has the meaning given in general formula 11; and n, R^2 , R^3 , X and Z have the meaning given in general formula 1.

10 15. Compounds of general formula 15,



wherein R^6 has the meaning given in general formula 11.

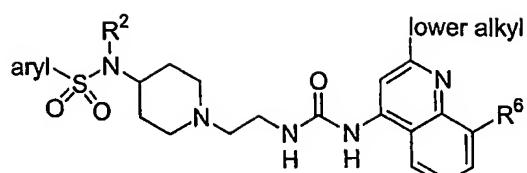
16. Compounds of general formula 16,



15

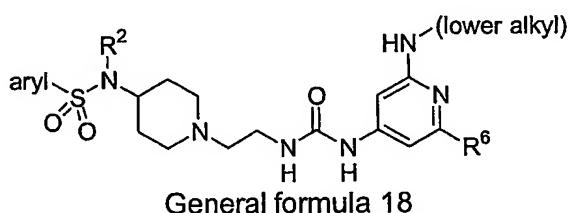
wherein R^6 has the meaning given in general formula 11.

17. Compounds of general formula 17,



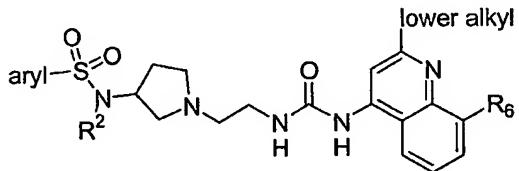
wherein R^6 has the meaning given in general formula 11; and R^2 has the meaning given in general formula 1.

5 18. Compounds of general formula 18,



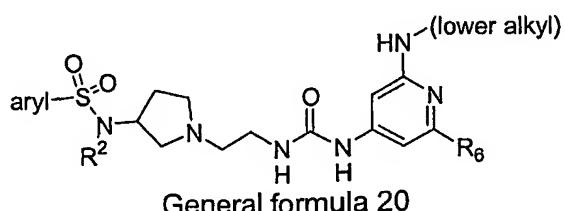
wherein R^6 has the meaning given in general formula 11; and R^2 has the meaning given in general formula 1.

10 19. Compounds of general formula 19,



wherein R^6 has the meaning given in general formula 11; and R^2 has the meaning given in general formula 1.

15 20. Compounds of general formula 20,



wherein R^6 has the meaning given in general formula 11; and R^2 has the meaning given in general formula 1.

21. The compound according to any one of claims 1 to 20 that is selected from the group consisting of

N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethyl-benzenesulfonamide

5 N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

Thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide

10 3-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

3,N-Dimethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

2-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

15 2,N-Dimethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

4-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide

20 4-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

4,N-Dimethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

2-Fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

25 2-Fluoro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

- 3-Fluoro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 4-Fluoro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 5 4-Cyano-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
- 3-Methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-pyrrolidin-3-yl)-benzenesulfonamide
- 10 3-Methoxy-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 4-Methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
- 4-Methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-pyrrolidin-3-yl)-benzenesulfonamide
- 15 4-Methoxy-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 3-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-pyrrolidin-3-yl)-benzenesulfonamide
- 3-Chloro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 20 4-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
- 4-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-pyrrolidin-3-yl)-benzenesulfonamide
- 25 2-Chloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-pyrrolidin-3-yl)-benzenesulfonamide

- Biphenyl-4-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide
- N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl})-pyrrolidin-3-yl)-4-propyl-
benzenesulfonamide
- 5 N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-pyrrolidin-3-yl)-4-
propyl-benzenesulfonamide
- Naphthalene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-
piperidin-4-yl)-amide
- 10 Naphthalene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-
pyrrolidin-3-yl)-amide
- Naphthalene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-
ethyl})-pyrrolidin-3-yl)-amide
- Naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-
piperidin-4-yl)-amide
- 15 Naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-
pyrrolidin-3-yl)-amide
- Naphthalene-1-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-
ethyl})-pyrrolidin-3-yl)-amide
- Quinoline-8-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-
20 pyrrolidin-3-yl)-amide
- Quinoline-8-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-
ethyl})-pyrrolidin-3-yl)-amide
- 4-tert-Butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-pyrrolidin-3-yl)-
benzenesulfonamide
- 25 4-tert-Butyl-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-
pyrrolidin-3-yl)-benzenesulfonamide

N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethyl-benzenesulfonamide

N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethyl-benzenesulfonamide

5 N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-trifluoromethyl-benzenesulfonamide

N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-trifluoromethyl-benzenesulfonamide

10 N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-trifluoromethyl-benzenesulfonamide

N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-3-trifluoromethyl-benzenesulfonamide

3,4-Dichloro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide

15 3,4-Dichloro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-pentyl-benzenesulfonamide

20 N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-pentyl-benzenesulfonamide

N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-pentyl-benzenesulfonamide

4-Butoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

25 4-Butoxy-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

- 4,5-Dichloro-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide
- 4,5-Dichloro-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide
- 5 4,5-Dichloro-thiophene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide
- 4-(3-Chloro-2-cyano-phenoxy)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
- 10 4-(3-Chloro-2-cyano-phenoxy)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 4-(3-Chloro-2-cyano-phenoxy)-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- N-[4-Methyl-5-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)sulfamoyl]-thiazol-2-yl]-acetamide
- 15 3-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
- 3-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 20 3-Bromo-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
- 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 25 4-Bromo-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-2-trifluoromethoxy-benzenesulfonamide

N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethoxy-benzenesulfonamide

5 N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethoxy-benzenesulfonamide

N-Methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-4-trifluoromethoxy-benzenesulfonamide

10 5-Dimethylamino-naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide

5-Dimethylamino-naphthalene-1-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide

5-Dimethylamino-naphthalene-1-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide

15 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide

20 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide

4-Bromo-2-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide

4-Bromo-2-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

25 4-Bromo-2-ethyl-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

- N-[5-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-ylsulfamoyl)-thiophen-2-ylmethyl]-benzamide
- N-[5-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-ylsulfamoyl)-thiophen-2-ylmethyl]-benzamide
- 5 N-{5-[Methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-sulfamoyl]-thiophen-2-ylmethyl}-benzamide
- 4-Benzenesulfonyl-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide
- 10 4-Benzenesulfonyl-thiophene-2-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide
- 4-Benzenesulfonyl-thiophene-2-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide
- 15 2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide
- 2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid methyl-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-amide
- 20 2-Phenyl-ethanesulfonic acid (1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide
- 4-Chloro-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 4-Bromo-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
- 25 1-{2-[4-(3-Biphenyl-2-yl-ureido)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[3-(3-Biphenyl-2-yl-ureido)-pyrrolidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{4-[3-(2-Isopropyl-phenyl)-ureido]-piperidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

5 1-(2-{3-[3-(2-Isopropyl-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-Methyl-quinolin-4-yl)-3-(2-{3-[3-(2-phenoxy-phenyl)-ureido]-pyrrolidin-1-yl}-ethyl)-urea

10 N-(1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-naphthalen-1-yl-acetamide

2-(4-Bromo-phenyl)-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide

4-Benzoyl-N-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzamide

15 1-(2-Methyl-quinolin-4-yl)-3-[2-(4-phenyl-piperidin-1-yl)-ethyl]-urea

1-(2-Methyl-quinolin-4-yl)-3-[2-(4-o-tolyl-piperidin-1-yl)-ethyl]-urea

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

20 1-[2-(4-Hydroxy-4-phenyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[2-(Benzyl-methyl-amino)-pyridin-4-yl]-3-[2-(4-benzyl-piperidin-1-yl)-ethyl]-urea

22. The compound according to any one of claims 1 to 20 that is selected from the group consisting of

4-Bromo-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide

5 4-Bromo-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-N-propyl-benzenesulfonamide

10 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-N-propyl-benzenesulfonamide

4-Bromo-N-isobutyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide

4-Bromo-N-isobutyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

15 4-Bromo-N-butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide

4-Bromo-N-butyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

20 N-Benzyl-4-bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide

N-Benzyl-4-bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide

4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-N-phenethyl-benzenesulfonamide

25 4-Bromo-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-N-phenethyl-benzenesulfonamide

- 4-Bromo-N-methyl-N-((R)-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 4-Bromo-N-ethyl-N-((R)-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 5 4-Bromo-N-ethyl-N-((S)-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 4-Bromo-N-methyl-N-((S)-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-pyrrolidin-3-yl)-benzenesulfonamide
- 10 N-Ethyl-3-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-piperidin-4-yl)-benzenesulfonamide
- N-Ethyl-4-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-piperidin-4-yl)-benzenesulfonamide
- N-Ethyl-2-methyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-piperidin-4-yl)-benzenesulfonamide
- 15 3-Chloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-piperidin-4-yl)-benzenesulfonamide
- 2-Chloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-piperidin-4-yl)-benzenesulfonamide
- 4-Chloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-piperidin-4-yl)-benzenesulfonamide
- 20 N-Ethyl-4-fluoro-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-piperidin-4-yl)-benzenesulfonamide
- N-Ethyl-4-methoxy-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-piperidin-4-yl)-benzenesulfonamide
- 25 3,4-Dichloro-N-ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl})-piperidin-4-yl)-benzenesulfonamide

N-Ethyl-N-(1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethyl-benzenesulfonamide

1-(2-Methyl-quinolin-4-yl)-3-{2-[4-(3-phenethyl-ureido)-piperidin-1-yl]-ethyl}-urea

5 1-[(S)-1-(4-Benzyl-piperidin-1-ylmethyl)-2-methyl-propyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[(S)-1-Benzyl-2-(4-benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

10 1-[(S)-1-(4-Benzyl-piperidin-1-ylmethyl)-3-methyl-butyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-cyclopropyl-quinolin-4-yl)-urea

1-{2-[4-(3-Methyl-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

15 1-{2-[4-(2-Methyl-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[4-(4-Methoxy-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

20 1-{2-[4-(4-Fluoro-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[4-(4-Bromo-benzylidene)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[4-(3-Methyl-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

25 1-{2-[4-(2-Methyl-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

- 1-{2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea
- 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-phenyl-amide
- 5 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid (2-chloro-phenyl)-methyl-amide
- 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide
- 10 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid methyl-phenethyl-amide
- 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-ethyl-amide
- 15 1-{2-[3-(2-Methyl-quinolin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid dimethylamide
- 4-Benzyl-1-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-ethyl-amide
- 1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methylamino-pyridin-4-yl)-urea
- 1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methylamino-pyridin-4-yl)-urea
- 20 23. Pharmaceutical compositions containing a compound of any one of claims 1 to 22 and usual carrier materials and adjuvants for the treatment of disorders which are associated with a dysregulation of urotensin II or urotensin II receptors, or disorders associated with vascular or myocardial dysfunction, comprising hypertension, atherosclerosis, angina or myocardial ischemia, congestive heart failure, cardiac insufficiency, cardiac arrhythmias, renal ischemia, chronic kidney disease, renal failure, stroke, cerebral vasospasm, cerebral ischemia, dementia, migraine,
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subarachnoidal hemorrhage, diabetes, diabetic arteriopathy, diabetic nephropathy, connective tissue diseases, cirrhosis, asthma, chronic obstructive pulmonary disease, high-altitude pulmonary edema, Raynaud's syndrome, portal hypertension, thyroid dysfunction, pulmonary edema, 5 pulmonary hypertension, or pulmonary fibrosis.

24. Pharmaceutical compositions containing a compound of any one of claims 1 to 22 and usual carrier materials and adjuvants for the treatment of disorders comprising restenosis after balloon or stent angioplasty, for treatment of cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, sickle cell acute chest syndrome, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, 10 addictions, schizophrenia, Alzheimer's disease, anxiety, obsessive-compulsive behavior, epileptic seizures, stress, depression, dementias, 15 neuromuscular disorders, or neurodegenerative diseases.

25. The use of one or more compounds of any one of claims 1 to 22 in combination with other pharmacologically active compounds for the treatment of hypertension, atherosclerosis, angina or myocardial ischemia, congestive heart failure, cardiac insufficiency, cardiac arrhythmias, renal 20 ischemia, chronic kidney disease, renal failure, stroke, cerebral vasospasm, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, diabetes, diabetic arteriopathy, diabetic nephropathy, connective tissue diseases, cirrhosis, asthma, chronic obstructive pulmonary disease, high-altitude pulmonary edema, Raynaud's syndrome, portal hypertension, thyroid dysfunction, pulmonary edema, pulmonary hypertension, or pulmonary fibrosis, restenosis after balloon or stent angioplasty, cancer, 25 prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, sickle cell acute chest syndrome, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular 30

or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, addiction, schizophrenia, Alzheimer's disease, anxiety, obsessive-compulsive behavior, epileptic seizures, stress, depression, dementias, neuromuscular disorders, or neurodegenerative diseases.

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- 10
26. The use of one or more compounds of any one of claims 1 to 22 in combination with other pharmacologically active compounds comprising ACE inhibitors, angiotensin II receptor antagonists, endothelin receptor antagonists, vasopressin antagonists, beta-adrenergic antagonists, alpha-adrenergic antagonists, vasopressin antagonists, TNF α antagonists, or peroxisome proliferator activator receptor modulators.
27. The method of treating a patient suffering from a disorder given in any one of claims 23 to 26 by administering a pharmaceutical composition according to any one of claims 23 and 24.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 02/13577

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D401/14 C07D471/04 A61K31/4709 A61P09/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| A | WO 01 45700 A (KNIGHT STEVEN DAVID ;SMITHKLINE BEECHAM CORP (US); WIDDOWSON KATHE) 28 June 2001 (2001-06-28) cited in the application claims 1,5 ----- | 1-27 |
| A | WO 01 45711 A (KNIGHT STEVEN DAVID ;SMITHKLINE BEECHAM CORP (US); DHANAK DASHYANT) 28 June 2001 (2001-06-28) cited in the application claims 1,4 ----- | 1-27 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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INTERNATIONAL SEARCH REPORT

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|---------------|-----------------|
| Internal ref. | Application No. |
| PCT/EP | 02/13577 |

| Patent document cited in search report | Publication date | | Patent family member(s) | | Publication date |
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